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ANNALS OF
INTERNAL MEDICINE

VOLUME 14 FEBRUARY, 1941 NUMBER 8

NEUROLOGICAL SYMPTOMS AND CLINICAL FINDINGS IN PATIENTS WITH CERVICAL DEGENERATIVE ARTHRITIS *

By STACY R. METTIER, M.D., F.A.C.P., and CHARLES S. CAPP, M.D.,
San Francisco, California

THE occurrence of pain and muscular stiffness about the neck and in the shoulder-girdle, and the radiation of pain down the arm or into the precordial region, has been the subject of considerable discussion in recent years. These symptoms may be readily explained when they are induced by a definite etiologic factor such as traumatic injury to the brachial plexus or pressure of cervical rib on this structure, bursitis, or the destruction of cervical vertebrae by bacterial or neoplastic processes. However, there are instances of pain which are not so easily explained and in which the origin is doubtful. In the medical literature one finds such conditions designated as radiculitis, pain of nerve-root origin, neuritis, or the "radicular syndrome" as described by Gunther and Kerr.[1]

Many years ago some of these symptoms were described by von Bechterew,[2] Strümpell,[3] Marie,[4] Bailey and Casamajor [5] and others, which they attributed to arthritic changes in the vertebral column. These authors, however, noted that there was no direct relationship between the amount of arthritic change and the degree of the neurologic manifestations.

In 1936, Hanflig [6] reported a group of 30 cases of radiculitis in which rigidity of the neck, pain, and other sensory and sometimes motor disturbances were the outstanding symptoms. In these cases, there was no evidence of local disease of the arm and shoulder, and he believed the pain was probably a manifestation of irritation or actual inflammation of cervical spinal nerve-roots due to cervical arthritis. He stated that the roentgenograms may or may not show evidence of hypertrophic changes.

In the same year, Turner and Oppenheimer [7] reported the results of their

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studies of the cervical spine in 50 patients with symptoms similar to those noted by Hanflig. They observed narrowing of the intervertebral discs which they held responsible for the symptoms whether hypertrophic arthritis was present or not.

Morton [8] reported three cases which showed the presence of hypertrophic spurs on the posterior aspects of the cervical vertebrae. These spurs, it was stated, projected into the spinal canal and caused pressure on the cord or encroachment on the cervical foramina, giving rise to symptoms.

In carrying out their studies, Turner and Oppenheimer and Morton used a special roentgenographic technic in which the posterior aspects of the vertebrae and the vertebral foramina were rendered visible by taking oblique projections of the spine.

The present study was undertaken to analyze the symptoms suggestive of cervical nerve-root origin occurring in patients presumably having osteoarthritis, and to attempt to correlate these symptoms with roentgenograms of the cervical vertebrae taken in the antero-posterior, lateral and oblique projections.

During the past few months, we have examined 30 patients with symptoms characteristic of cervical radiculitis. Most of the patients in this group were between 40 and 60 years of age. Three were under 40 years of age.

The symptoms complained of most frequently were pain, rigidity of the neck, and muscular weakness of the hand or arm. The onset of pain was usually abrupt and in many cases was first noticed by the patient on awakening in the morning. More often than not the pain was localized in and about the shoulder, especially about the insertion of the deltoid muscle, or radiated down the arm into the fingers. As a rule, these symptoms appeared months or even years before there were any complaints of neck discomfort. Usually the pain was unilateral but, with the exception of a few instances, it became bilateral at some time during the progression of the pathologic condition. The pain varied from one of an excruciating character to a dull, aching sensation. At times it was described as sharp, jabbing, needlelike and penetrating; at other times as a prickly or stinging feeling. Some patients complained only of numbness and tingling in the fingers or of a drawing or dead, aching sensation in the muscles of the arms.

The loss of freedom of use of one upper extremity was a common complaint. Many patients had become unable to comb their hair or to extend the arm behind the back to adjust their clothing. Others were unable to perform fine movements such as sewing or writing, and some of them found it difficult to grasp objects.

A few patients became conscious of pain in the neck during the early course of illness, but in most patients it was a late development. In no instance was there definite restriction of movement of the head and neck, but it was often stated that pain in the neck was induced by jarring of the body. The discomfort was sometimes described as a " headache at the base

of the brain," as a feeling of "congestion" at the base of the brain, or simply as muscular soreness.

In none of the patients examined was there evidence of atrophy of the muscles of the hands, arms or shoulder-girdle. In all instances the reflexes of the arm showed normal reactions.

Although the symptoms in these patients varied in degree, in their general character and distribution they were uniform enough to lead one to suspect the presence of a common underlying pathologic process. Such, however, was not the case in our experience, and therefore we are not in entire agreement with Turner and Oppenheimer who state, "If neurological symptoms existed in the patient and directed us toward examination of the cervical spine, there was a consistent finding of a narrowing of one or more of the intervertebral spaces regardless of whether we were dealing, in addition, with hypertrophic arthritis, infectious arthritis, or with traumatic displacement."

The demonstration of the presence or absence of arthritis in the cervical vertebrae in our 30 patients was determined by the roentgenographic findings. Accordingly, synovial swelling or inflammatory reaction in the soft tissue of the joints indicative of early changes was precluded by this method of examination. The cases were divided into three groups, depending upon the amount of alteration noted. In 18 patients, marked hypertrophic changes were observed. These consisted of circumferential osteophyte formation which projected into the intervertebral canals from the superior or inferior margins of the vertebrae, and caused from slight to marked narrowing of the foramina, depending on the size of the hypertrophic spurs. The osteoarthroses occurred more frequently on the left side than on the right. In addition, in the regions of exostoses, the intervertebral discs were thinned out, so that there was from slight narrowing to almost complete obliteration of the intervertebral spaces. The disc cartilage adjacent to small processes was not necessarily thinned out. It was noted with interest that the sites of predilection were between the fifth and sixth and the sixth and seventh vertebrae.

The symptoms elicited from the seven patients segregated in the second group were similar to those described above, but the roentgenographic findings of osteoarthroses were considered minimal in degree. In these seven patients, there was a minimal to slight degree of osteophyte formation on the adjacent surfaces of the vertebrae, usually the fifth and sixth. This small amount of arthritis was accompanied by narrowing of the intervertebral discs in only three patients. In most of the patients, there was some sclerosis of the articular facets.

In four patients with symptoms of radiculitis, there was no apparent abnormality of the articular facets in the roentgenograms, no evidence of proliferative new bone formation at the margins of the vertebrae, no noticeable narrowing of the intervertebral foramina or thinning of the intervertebral discs.

Case Reports

Case 1. D. D. DeL., a white American female 57 years of age, complained of pain in the shoulders and neck and weakness of both hands. She stated that six months prior to coming to the Out-Patient Department, she awakened one morning with a feeling that the left arm was dead and was conscious of numbness and tingling across the back of the thumb, index and middle fingers. During the course of the morning, the symptoms subsided, but subsequently were of daily occurrence. She found that lying on the left side increased her discomfort. About a week after the onset of her illness, similar symptoms appeared in the right arm and hand. Four weeks later she noticed some difficulty in grasping objects, particularly in attempting to use the curling-iron which, on occasions, actually fell from her hand. About two or three months ago she first noticed sharp, stabbing pains in both wrists which she stated " felt as though needles were being pushed through." At this time she noticed

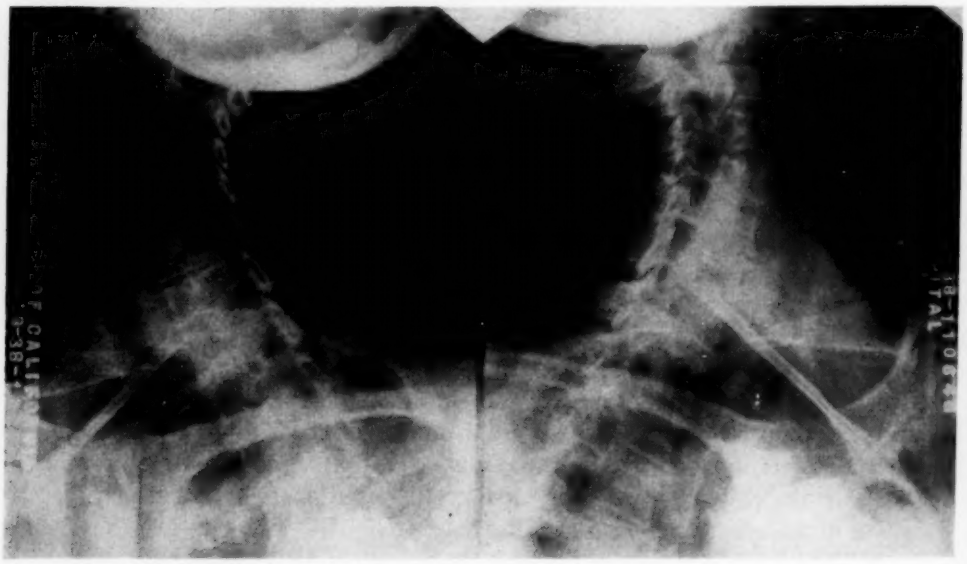

Fig. 1. *Case 1.* Shows narrowing of joint spaces between fifth and sixth, and sixth and seventh cervical vertebrae. Films were made from the oblique projection.

stiffness of the neck on awakening in the morning and "a sore feeling deep in the back of the neck." This soreness spread into the left shoulder. Her symptoms were aggravated by turning the neck, were alleviated by warmth and, as a rule, gradually subsided during the course of the day. At no time had there been an inability to raise her arms above the level of the shoulders.

Physical examination revealed no abnormalities of the reflexes of the upper extremities, and there was no evident atrophy of the muscles of the shoulder-girdle or hands. There was no swelling of the small joints of the hands. As the patient sat in the chair, she rubbed her hands constantly.

The roentgen findings revealed the following: " There is almost total obliteration of the intervertebral joint between the sixth and seventh cervical vertebrae. There is extreme narrowing of the intervertebral canal space by proliferative bone at the margins, more so on the left than on the right side. There is some narrowing of the intervertebral joint between the fifth and sixth vertebrae also. There is no evidence of cervical ribs nor of metastases nor of fracture or dislocation."

Case 2. E. P., a white female aged 45 years, complained of pain in the right shoulder and numbness and tingling in the fingers. She stated that for more than 10 years she had had pain recurring at frequent intervals in the right shoulder in the region of the insertion of the deltoid muscle. This was described as an aching sensation similar to a "toothache." This discomfort frequently awakened her about three o'clock in the morning and she learned that some relief could be obtained by the application of heat or by wearing a woolen sweater. About five years ago she became aware of numbness and tingling in the fingers of the left hand. Associated with the onset of this symptom, she noted a transient blanching of the fingers of both hands, followed by a short period when they appeared deep red in color. This phenomenon had occurred off and on since, and was noticed to appear more frequently during the winter months. For the past few months there had been pain and muscle stiffness in the left side of the neck, with radiation into the shoulder.

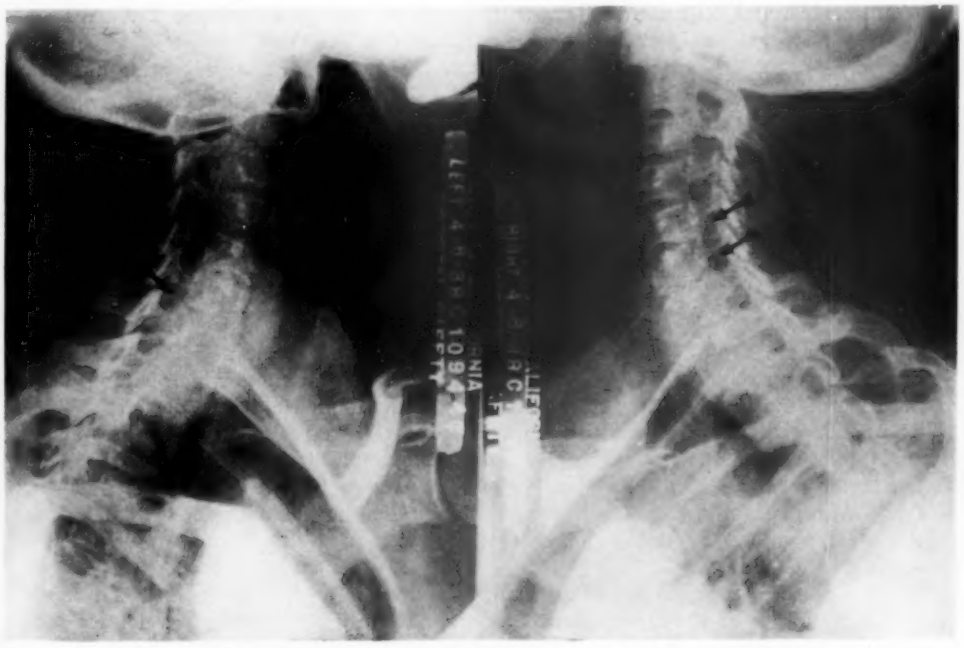

FIG. 2. *Case 2.* An oblique projection showing narrowing of the fifth and sixth, and sixth and seventh intervertebral discs. Note the encroachment on the intervertebral foramen by spur formation.

Physical examination revealed the patient to be slightly overweight. There were no other findings of significance.

Examination of the roentgen films was reported as follows: "The intervertebral discs between cervical 5 and 6 and 6 and 7 are narrowed. There is bony proliferative change encircling the margins of the discs particularly on the lateral side of the posterior edges so that there is encroachment by the spur formations on the intervertebral foramen, particularly the sixth foramen on the left side and the seventh foramen on the right side. There is a left lateral scoliosis involving the lower three cervical vertebrae and the upper five thoracic vertebrae. The greatest convexity is toward the left, being at the level of thoracic 4. There is no evidence of cervical ribs."

The following case is reported as an example of the radicular syndrome with roentgen findings of a minimal amount of arthritis.

Case 3. C. B., a white American female, aged 57 years, complained of pain in the right shoulder. For the past five years, the patient had had recurring pain in the region of the right deltoid muscle. This was described as a sharp, stabbing pain and was accompanied by a constant dull, aching feeling. Soon after the onset of symptoms she found it difficult to put her hand behind her back to tie her apron-strings or to elevate her arm to comb her hair. In addition, there were numbness and tingling of the finger-tips which extended up into the wrist. She was frequently awakened about 3 or 4 o'clock in the morning by these symptoms, especially when she slept on the right side of the body. About three months ago, similar symptoms appeared in the left arm and hand. About one month ago she began having a tired, aching pain between the shoulder-blades which radiated into both shoulders. All of her symptoms were most marked on awakening in the morning, but she found that she could obtain some relief on applying heat at the back of the neck, rubbing her arms with hot water or moderately exercising the muscles of the neck.

The physical examination revealed nothing of significance excepting moderate hyperesthesia of the skin of the hands.

Roentgenographic examination showed the following: "there is no noticeable narrowing of the intervertebral discs. There is only a very minimal degree of marginal osteophyte formation on the superior and inferior edges of the fifth cervical vertebrae. There is no sclerosis of the articular facets."

The following case history is reported as an example of the radicular syndrome but without roentgenographic evidence of cervical osteoarthritis:

Case 4. I. M. C., a white American female, formerly a housewife and now employed as a waitress, complained of pain in the left side of the neck. This pain was described as an aching sensation accompanied by muscle soreness which extended from the base of the neck into the occipital region and radiated out into the left shoulder. These symptoms were first noted about three years ago, and soon after their appearance there were numbness and tingling in the thumb and index finger of the left hand. On occasions there had been blanching of the fingers followed by reddish discoloration. More recently, there had been a drawing sensation in both sides of the neck. Relief is obtained by taking a hot bath or with moderate exercise. Jarring will aggravate the symptoms.

On physical examination, the patient appeared slightly underweight. There were no abnormalities of the reflexes of the upper extremities, but there was definite spasm of the left trapezius muscle. There was no evident swelling of the small joints of the hand, no focal tenderness over the bursa of the shoulder, and the symptoms of the scalenus anticus syndrome were not induced by rotation of the head to the affected side or by pressing down on the shoulder.

Roentgen-ray: "There is no evidence of any abnormality from a bony standpoint, nor evidence of cervical rib. The intervertebral foramina are not narrowed, and there is no evidence of proliferative bony changes at the joint margins."

Discussion

The first two case histories reported here were selected from a group of 17 patients having similar symptoms presumably of nerve-root origin. In these patients there was definite evidence of degenerative arthritis of the cervical vertebrae. The roentgenograms taken in the oblique projection

showed narrowing of the intervertebral foramina by the ingrowth of the marginal osteophytes. The decrease in vertical diameter of the foramina was furthered in many instances by close approximation of the vertebral bodies due to thinning of the intervertebral discs. It is evident from this study that the combination of these two processes may impinge upon the nerve trunk as it passes through the involved foramina or may affect the sympathetic fibers controlling blood flow.

One wonders, however, why this process is able to pick out the sensory fibers in such a high percentage of cases, and not involve the motor fibers at the same time. A possible explanation for this is the fact that the motor fibers of the anterior cervical roots are fewer in number and comprise a bundle only one-third the size of the posterior sensory fibers.[9] This leads us to the conclusion that actual diminution in the size of the nerve trunk may be sufficient to give rise to the irritative phenomena recognized clinically as the radicular syndrome.

It seems unlikely that a similar process can adequately explain the neurologic symptoms arising in the patients of the second and third groups. In our roentgenograms there was no radio-opaque material present in the intervertebral foramina to suggest impingement upon a nerve bundle. Nathan [8] in 1916 induced experimental non-suppurative arthritis in animals and noted thickening of the periosteum of the vertebrae. From his studies he concluded that these changes could lead to irritation and compression of nerve roots. Whether or not the sequence of events in man may consist of a preliminary swelling in the periosteum of the cervical vertebrae similar to that produced in the experimental animal, and finally in the formation of new bone, is a matter of speculation. It is hoped that further studies on this problem may be carried out in conjunction with members of the Department of Anatomy.

Viewing the subject from the standpoint expressed by Turner and Oppenheimer that narrowing of the intervertebral spaces was a common lesion in their patients, we were unable to arrive at identical conclusions. We do not doubt the results these authors obtained but do disagree with the statement that narrowing of the intervertebral discs may be a consistent finding, or may be the first change of importance before the development of hypertrophic arthritis.

It is important to emphasize that this syndrome is of relatively frequent occurrence and, as a rule, inadequately treated. This group of 30 patients was seen by us during a period of less than three months. Many of the patients had wandered from one clinic to another in an endeavor to get relief from their symptoms. Many had resorted to forms of treatment not regularly recognized by the medical profession. It was of interest to learn that those who had received a special form of treatment that was basically manipulative in nature had definite relief from their discomfort.

In our clinic, treatment has consisted of heat to the neck, massage, manual

traction and manipulation. The majority of patients are relieved of pain on this regime.

Summary

This syndrome of pain and muscular stiffness about the neck and in the shoulder-girdle, or the radiation of pain down the arm, is of relatively frequent occurrence in persons beyond 40 years of age. From our studies it was learned that in approximately two-thirds of the patients there was roentgenologic evidence of hypertrophic arthritis. In the remaining patients there was no evidence of arthritis or of any other pathologic process in the roentgen-ray films. The value of taking roentgen-ray films in the oblique projection is emphasized. The patients were greatly relieved of their symptoms by the application of heat, massage, manual traction and manipulation, and posture training.

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STUDIES IN THE CELLULAR EXUDATES OF BOWEL DISCHARGES. III. THE DIAGNOSTIC SIGNIFICANCE OF CELLULAR EXUDATE STUDIES IN CHRONIC BOWEL DISORDERS *

By Z. Bercovitz, M.D., F.A.C.P., *New York, N. Y.*

The purpose of this paper is to give the practical applications of the findings of a series of studies of the cellular exudates of bowel discharges.

The microscopic examination of bowel discharges for the presence or absence of cells affords the general practitioner a very simple, yet most effective method of determining whether or not there are pathological changes in the bowel wall. The presence of cells in the bowel discharges indicates that pathological changes are taking place. This knowledge is of particular value when following the progress of an inflammatory lesion. The decrease of cells found in the bowel discharges shows that healing is taking place. Thus when cells cease to appear in the bowel discharge, the physician will know that an active pathological condition no longer exists.

The information obtained from cellular exudate studies makes it possible for the practitioner to determine whether a diarrheal condition is related to a breakdown in the bowel wall, such as occurs in chronic ulcerative colitis, or whether it is functional and nervous in origin. When patients with diarrhea are not suffering from pathological change in the bowel wall, cells will be absent from their bowel discharges. This will be true even if the patient is given a saline cathartic, an enema or a colonic irrigation.

Materials and Methods

Three types of specimen are generally examined for cellular exudates. These are (1) the normal fecal movement, from which the outside of the mass should be selected because it comes into closer contact with the mucosa and may therefore contain the cellular exudate; (2) the watery discharge which follows a saline cathartic. This is one of the most valuable types of specimen that can be obtained for examination. The patient is given the same preparation for this examination as for the diagnostic study of the stools for chronic amebic dysentery. A dose of epsom salts or of some other saline cathartic should be given, and the patient should be instructed to come to the physician's office to evacuate the bowels. He should discard the major portion of the watery evacuation, but should collect the last of the movement

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that is forced out. This type of specimen is particularly valuable because it may contain cells from pathological areas higher up in the bowel which would be missed if the normal fecal movement only were examined. And finally (3) the terminal mucus evacuated following three normal saline enemas should be collected for microscopic examination. This is by far the most valuable type of specimen to obtain for cellular exudate study because the gross fecal matter is washed away with the first two saline enemas, while mucus only is evacuated after the third. The patient should be instructed to take three enemas, which should follow each other without delay, but he should be warned not to insert the enema tip more than about one or two inches within the sphincter. Otherwise he might cause injury to the bowel wall. The new sigmoid cannula described by Bercovitz [1] can be used to aspirate the terminal mucus in cases where the patient is to have a sigmoidoscopy.

A small amount of the bowel discharge should be emulsified on a glass slide in a drop of Loeffler's methylene blue and should be covered with a coverslip. The cells will take up the methylene blue in this type of preparation so that the cytoplasm will appear as a delicate pale blue while the nuclei will stand out as either solid or ringed bodies within the cell structure. When making the wet coverslip preparation with methylene blue, it is important to make sure that the preparation is carefully emulsified with the dye, and when the coverslip is placed on this emulsion to make sure that it is thin enough so that large black print can be seen through it.

If it is desired to make a permanent preparation, the bowel discharge should be smeared onto a clean glass slide and should then be immersed immediately in warm Schaudinn's fluid. From this point onwards, the staining technic is that which is ordinarily used for making the permanent saline preparations for intestinal protozoa. (Details given by Bercovitz.[2])

When specimens have been fixed in formalin and embedded in paraffin, the appearance of the cells will differ from when the specimens have been prepared with the methylene blue or with Schaudinn's solution and stained with Heidenhain's iron hematoxylin technic. A certain amount of shrinkage takes place with the paraffin technic which causes the cells to appear smaller and quite compact, while as a rule the nuclei appear to be solid. This appearance is due to the fact that the hematoxylin stain is taken up as a solid mass. With the wet methylene blue coverslip preparations as well as with the permanent preparations made with Heidenhain's iron hematoxylin technic, the cells retain their natural size and shape so that it is possible to make careful detail studies of the cytoplasm and the nuclei in order to determine what changes may be taking place within the structure of the cell.

Cytology of Exudates

When specimens are prepared according to the technic outlined, four main types of cell may be found in the bowel discharge upon microscopic examination. Some of these cells are frequently confused with the protozoa of dysentery, but should be clearly differentiated from them.

Epithelial cells generally assume irregular shapes, although they may be oval to round or square. They are sharply defined and can be distinguished readily from the rest of the cellular exudate. The cytoplasm, which is easily seen, is usually quite smooth or finely granular, but it may also contain coarse granules which stain dark. The nuclei of epithelial cells usually appear as open rings and seem to be composed of nuclear membrane, which may be delicate or coarse, on the inner surface of which there either may or may not be beading with granules of different sizes. It is not uncommon to find heavy granules within these open-ringed nuclei. As a rule the centrosome may also be distinguished readily, while upon occasion very delicate lines of chromatin matter may be observed which seem to extend from the centrosome to the nuclear membrane. Since many forms of epithelial cells have been mistaken for amebae, it is necessary to distinguish between them very carefully. (Figure 1.)

Polymorphonuclear leukocytes usually constitute the majority of the cells found in a cellular exudate specimen. However, they assume an entirely different appearance from the polymorphonuclear leukocytes which may be seen in a blood film stained with Wright's or Leishman's modification of the Romanowsky stain. The nuclei, in either the segmented or the young forms, most commonly appear as heavy rings within the cytoplasm of the cell. At times these rings are lined with coarse chromatin beads and a centrosome may be visible. If the fine adjustment of the microscope is focused up and down carefully, it will be possible to observe these rings at different levels within the cell proper. Usually there are three such rings, and with a little experience they can be differentiated from the cysts of protozoa, with which they are most frequently confused. The differential diagnosis will be given when the protozoa which cause dysentery are described.

Polymorphonuclear leukocytes are readily seen in saline smears of the bowel discharge, even when no stain is used. In some cases when the methylene blue stain is used, it will be found that the nuclei of the polymorphonuclear leukocytes absorb the stain. They then appear as solid masses, and present the more commonly recognized picture of this cell. At the present time it is not known exactly what conditions favor the different appearances of the polymorphonuclear leukocytes. In a few instances, some eosinophiles have been observed when wet preparations with Wright's stain have been used. Further work on eosinophiles in the bowel discharges is now in progress (and will supplement this study as soon as it is completed).

Round cells belonging to the lymphocytic series are frequently seen. These cells are usually much smaller than the polymorphonuclear leukocytes. In shape they are round to oval, and have a nucleus which may be either ringed or solid and which takes up the greater part of the cell.

Macrophage cells of endothelial origin are quite commonly seen, especially in cases of bacillary dysentery. In the fresh unstained preparation, these cells are the most striking in the whole field. They are large and

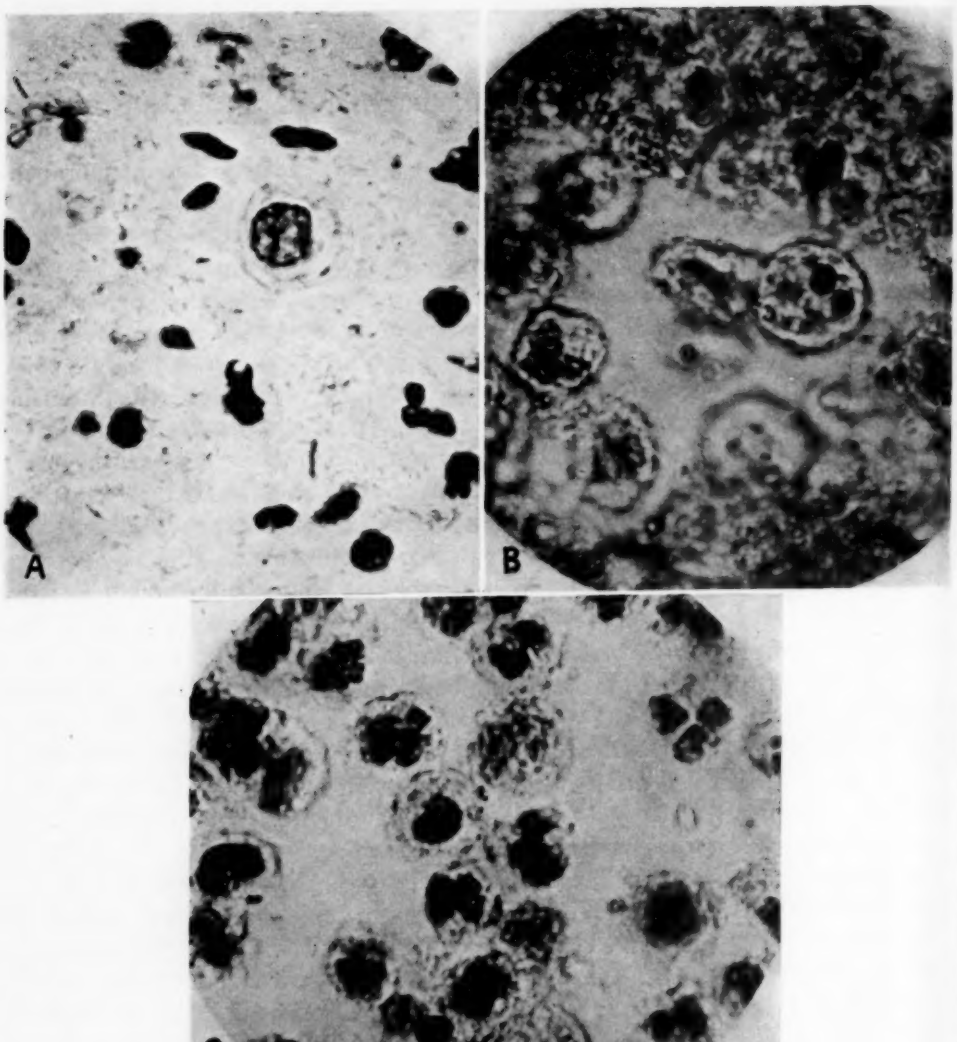

FIG. 1. Cellular exudates from patients with chronic ulcerative colitis. *A*. Note epithelial cell with ring nucleus. *B*. Note two epithelial cells stuck together. *C*. Note different types of polymorphonuclear cells. Loeffler's methylene blue wet preparations; oil immersion.

prominent, with well-defined ectoplasm and nucleus. At times the cytoplasm is vacuolated and may contain ingested particles such as yeast cells, bacteria, or even red blood cells. These cells may develop to an enormous size and some of them have measured more than 100 microns.

THE DIFFERENTIAL DIAGNOSIS OF AMEBIC AND BACILLARY DYSENTERY

Through the brilliant work of Manson-Bahr and his collaborators, as well as of Wenyon and O'Connor, a clear differentiation has been established

between the stools in amebic and in bacillary dysentery. Within the space of a few years, the differences in the stools in these two types of dysentery, which these men had pointed out, were amply demonstrated by men such as Graham, Willmore, Shearman and Anderson, whose work covered the fields of bacteriology, cytology and pathology.

In amebic dysentery, the bowel discharge consists mainly of mucus, which at times is streaked with blood. This discharge has the appearance of a clear, glairy substance, much like the white of an egg. It is generally quite copious in amount, flows freely in the bed-pan, and is difficult to pick up with an applicator. As a rule, it contains a scanty cellular exudate. Evidence may be found of proteolytic digestion of the cells, beginning at the periphery and affecting the nucleus last of all. Clearly defined bodies, about 20 microns in diameter, may be observed scattered among the mucus. If these bodies are watched closely, even under the low power objective, such characteristics as definite changes in shape and progressive motility will be noticed. If the fresh, unstained preparation is examined with the high dry objective or the oil immersion, it will be observed that there is pseudopodia formation with clear differentiation between the ectoplasm and the endoplasm. The nucleus, however, cannot be visualized. This fact constitutes one of the most important differential characteristics of the freshly passed *Endameba histolytica*.

Bacillary dysentery bowel discharge is characterized by a heavy cellular exudate. Cells of all kinds will be found. Polymorphonuclear leukocytes will predominate, but there will also be a few red blood cells, lymphocytes, epithelial cells, plasma cells and endothelial macrophages. It is important to recognize the endothelial macrophages because they seem to resemble free-resting amebae, and are consequently confused with them. These cells are larger than the polymorphonuclear leukocytes and are the macrophages of endothelial origin which were described by Manson-Bahr and his associates. There is usually some vacuolization in these cells, and in the fresh, unstained preparation the nucleus stands out prominently as a heavy ring with beading. It should be observed, however, that the macrophages of endothelial origin have no progressive motility, and any motion that may be seen will be of a pulsating type.

On the basis of these findings, it will be possible to make a provisional differential diagnosis of amebic and bacillary dysentery.

Cellular Exudate Studies and Findings

During the past four years extensive observations have been made of patients who were free from gastrointestinal disorders and also of patients who had definite bowel complaints in order to determine, if possible, the diagnostic significance of the absence or presence of cellular exudates in bowel discharges.

The initial investigations of this study were concerned with the problem

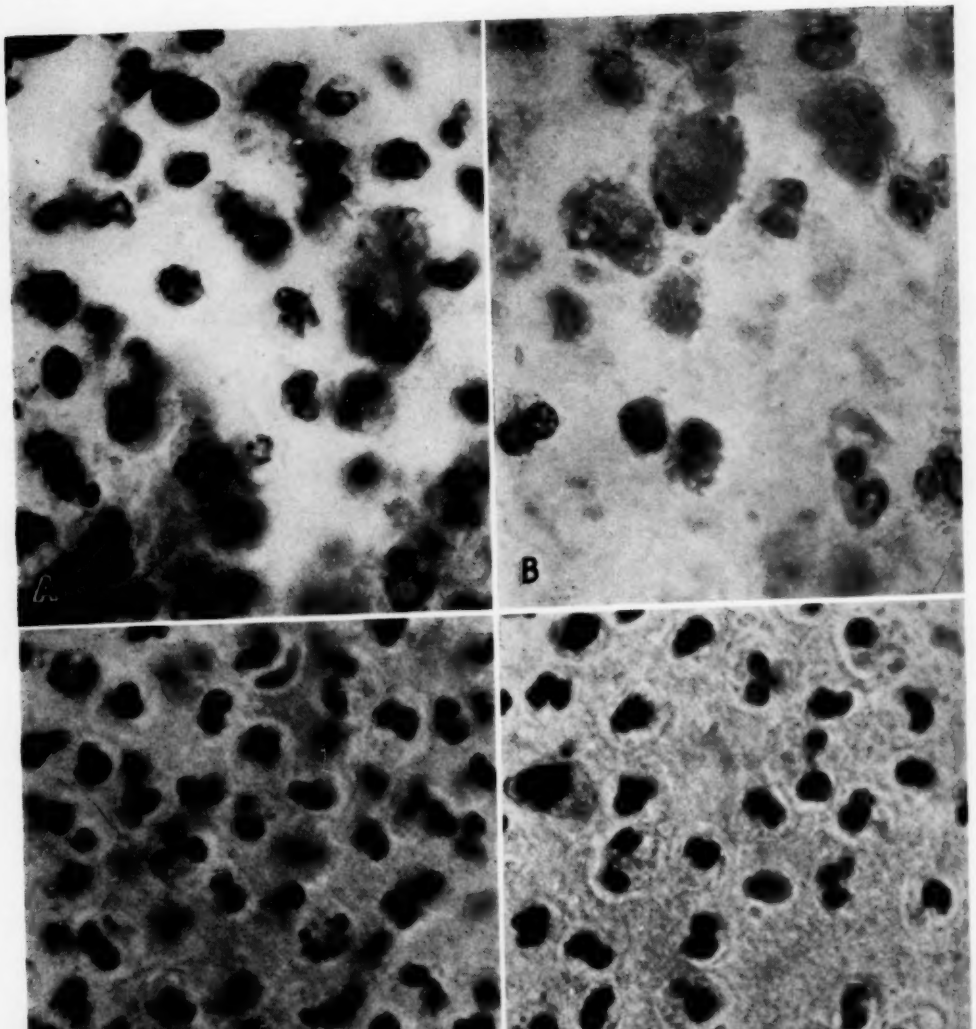

FIG. 2. Cellular exudates from patients with bacillary dysentery (Flexner). Note predominance of polymorphonuclear cells with ringed nuclei (*A*, *B*, *C*) as compared with *D*, in which the polymorphonuclear cells have more solid nuclei. Loeffler's methylene blue, wet preparations; oil immersion.

as to whether or not cellular exudates should be expected in the discharges of the normal bowel mucosa. Control observations were made of 1123 patients who stated that they had no disorders which could be referred to the

gastrointestinal tract. Altogether 2158 specimens were examined from these so-called normal patients and, with the exception of 11 specimens, all were negative for cells. The 11 positive specimens came from two patients, 57 and 62 years of age, who unfortunately could not be traced for subsequent study. Of the 2158 specimens, 198 were diarrheal movements following dosage with epsom salts.

In order to see whether negative findings would be true whenever pathological change was not present in the bowel mucosa, specimens were obtained at the autopsies of seven individuals. These specimens were taken from several different levels in the gastrointestinal tract, and at the same time scrapings were obtained from the bowel wall at the same locations. Cells of the same type were found in the specimens and in the scrapings, but as they were not the type of cell ever found in the bowel discharges of living persons, it was presumed that they were the result of postmortem degeneration. To check this conclusion, three dogs were given lethal doses of sodium amytal, and their abdomens were opened as soon as respiration ceased. Specimens of the bowel contents from three locations in the colon and also from the terminal ileum were taken for examination, and were found to be negative for cells.

With uniformly negative results for normal bowel mucosa, it was possible to assert that when cells were absent from the bowel discharges, no pathological condition would be found to exist in the bowel mucosa. But in order to discover the relationship of cellular exudates in bowel discharges to pathological conditions in the bowel mucosa, a careful study was made by Bercovitz and Fuller [3] of 216 patients who were suffering from various types of bowel complaint.

Of the 216 patients studied, it was found that 66.2 per cent had positive cellular exudates. An analysis of the most important symptoms associated with the various types of bowel complaint found in these patients shows that with pus the positive cellular exudate was 100 per cent; with blood in the stools, 86.9 per cent; with diarrhea, 84.2 per cent; with tenesmus, 83.3 per cent; with alternating diarrhea and constipation, 73.9 per cent; with mucus in the stools, 68.8 per cent; and with constipation, 50 per cent. As these symptoms, with their high percentages for cellular exudates, are associated with definite and progressive pathological conditions which can be identified by sigmoidoscopic and, if necessary, roentgen-ray examinations, it is clear that the cellular exudate study should be made a routine procedure whenever a patient with a bowel complaint reports the presence of any of these symptoms.

Case Histories

So that the practical diagnostic significance of these cellular exudate studies may be brought out more clearly, groups of case histories have been selected which will be illustrated with photomicrographic slides of the cellular

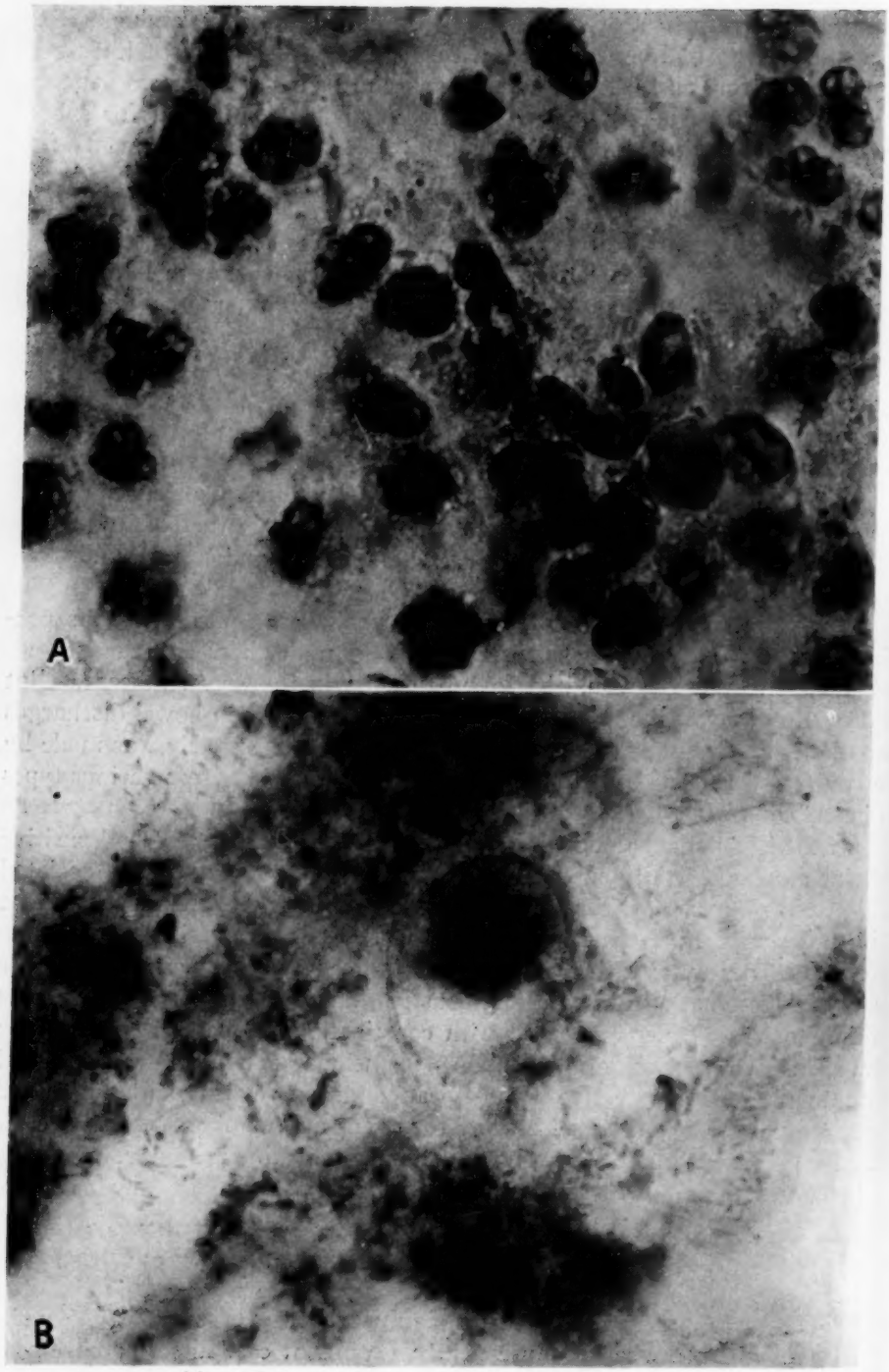

FIG. 3. Exudates of bacillary dysentery compared with amebic dysentery. *A*. Bacillary dysentery (Flexner). Loeffler's methylene blue wet preparation. Note heavy cellular exudate of polymorphonuclear leukocytes and denuded epithelial cells. *B*. Amebic dysentery. Wet fixation in Schaudinn's fluid, Heidenhain's iron-hematoxylin stain. Note trophozoite of *Endameba histolytica* and lack of cellular exudate as compared with *A*. Oil immersion.

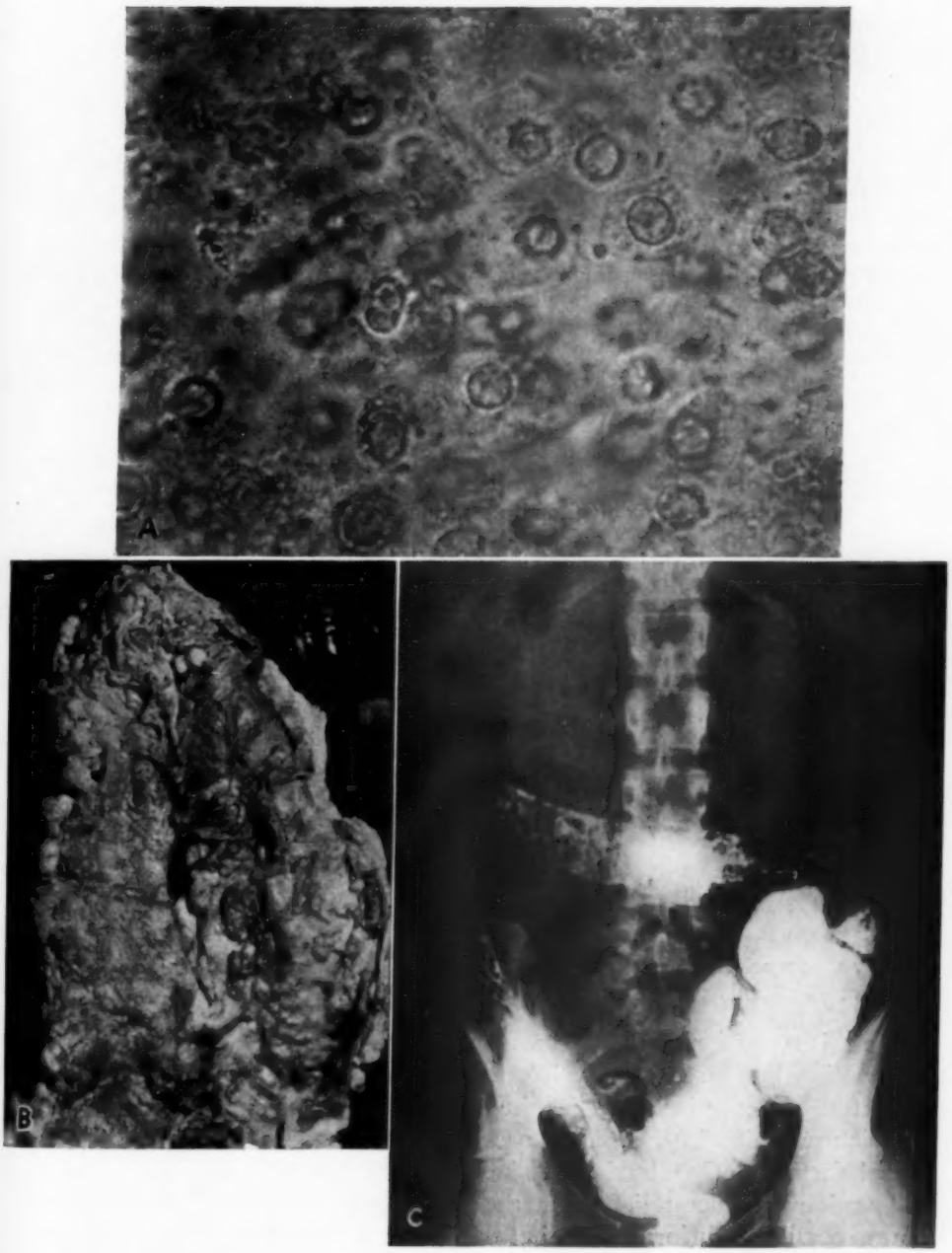

FIG. 4. Chronic ulcerative colitis with hypertrophic polypoid changes. *A*. Cellular exudate in bowel discharge. Loeffler's methylene blue wet preparation. Note irregularly shaped epithelial cells with heavy ringed nuclei. *B*. Autopsy specimen showing polypoid changes in bowel wall. *C*. Barium colon enema roentgenogram.

exudates as they occurred, and in some cases with copies of roentgenograms, photographs of autopsy specimens and surgical specimens. These are all original.

Group I

Chronic Ulcerative Colitis with Hypertrophic Polypoid Changes.

Female, aged 22. Four days post-partum, there was sudden onset of diarrhea, 30 to 40 times daily and of hectic fever. Seen for the first time on July 3, 1937, twelve weeks after the onset. There was a heavy cellular exudate of polymorphonuclear leukocytes, and macrophage cells were scattered throughout. The patient continued to have a stormy course, with diarrhea varying from 4 to 5 bowel movements to 15 or 20 in the 24 hours. Four months later, stool examinations still showed a heavy cellular exudate (figure 4) composed chiefly of large irregular-shaped cells with prominent vacuolated nuclei. The clinical condition was essentially the same, except for the fact that the patient's general condition was worse than before. The roentgenologic conclusion, following a barium colon enema on November 16, 1937, was an ileo-colitis with advanced hypertrophic and chronic inflammatory changes as well as probable multiple ulcerations. At autopsy, the colon was found to be markedly hypertrophic with numerous polypi and ulcerations.

This case is typical of the results of cellular exudate studies in cases of chronic ulcerative colitis with hypertrophic changes in the mucosa. In two of the cases, autopsy specimens confirmed the diagnosis made before death.

Group II

Patients with Diarrhea and Negative Cellular Exudates.

Female, aged 42, complaining of diarrhea. This patient is the unhappy wife of a man who makes frequent trips to Europe without her. The symptom of diarrhea begins when her husband sails. She is actively interested in a large number of civic and welfare organizations. She noted that her menstrual periods were irregular and that she had frequent hot flashes. Five watery specimens of bowel discharge, following a dose of epsom salts, were negative for cells when examined. Sigmoidoscopy showed that the mucosa of the rectum was atrophic, but further up in the sigmoid, the atrophy was much less pronounced. Fluid aspirated through the sigmoidoscope with the sigmoid cannula was also negative for cellular exudates.

In this type of case, the patients complain of diarrhea of varying degrees of severity, but careful study has failed to reveal the presence of cellular exudates. In each instance, definite elements of stress and strain enter into the picture which in themselves are sufficient to be definitely related as a causal factor to the diarrhea. The administration of sedatives has been followed by prompt relief from the symptoms in each of these patients. It was possible to inform them that they had no ulceration of the bowel, and that the diarrhea was of a type related to nervous stress and strain and was not of the type found in ulcerative colitis. The lack of cells in the diarrheal discharges eliminates the possibility of cancer, and this is of importance to the physician because many patients form an idea that they may have cancer.

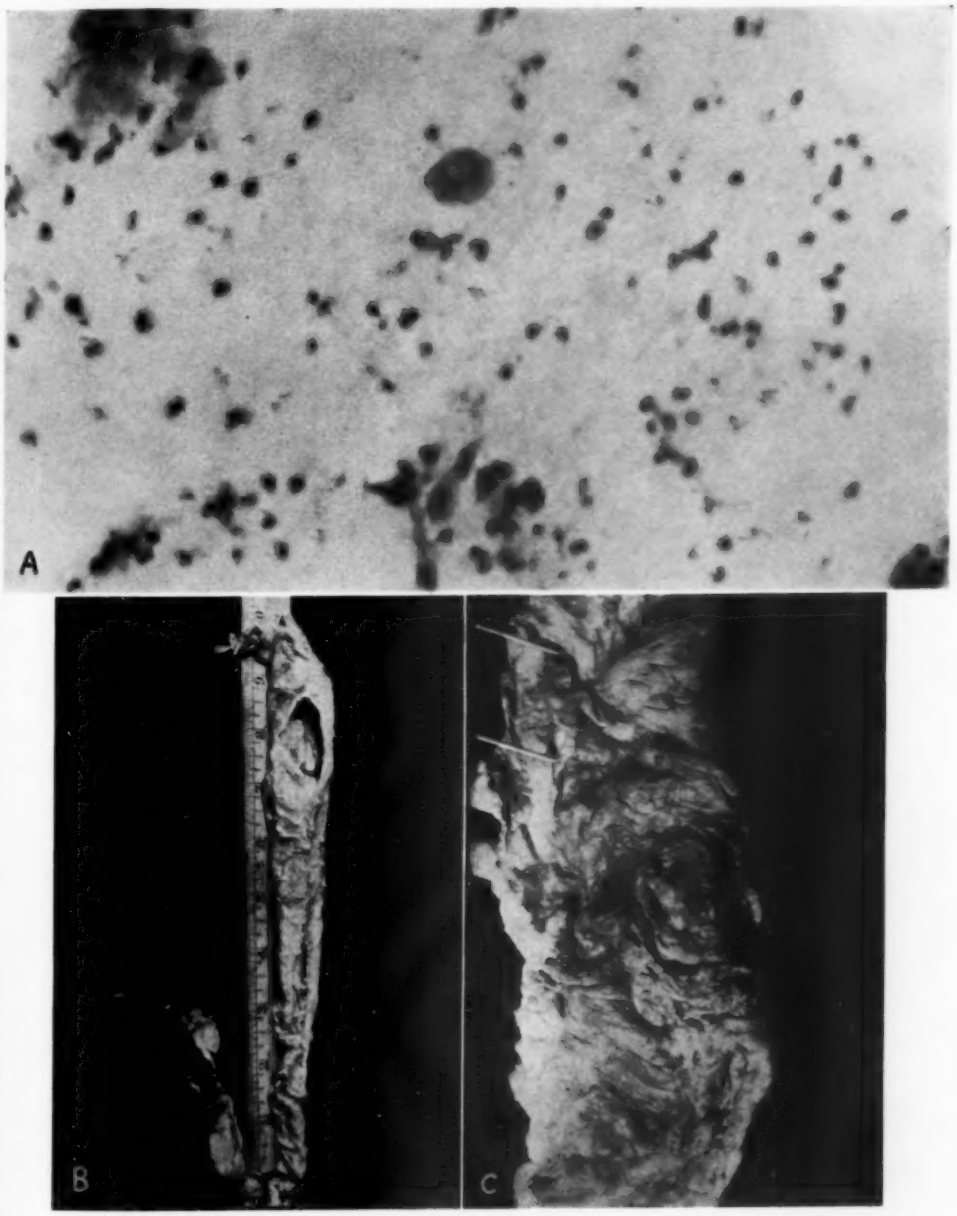

FIG. 5. Acute amebiasis complicated by perforation. *A*. Bowel discharge showing moderately heavy cellular exudate with *Endameba histolytica*. Wet fixation in Schaudinn's fluid iron hematoxylin stain; high dry. *B*. Cast of bowel passed by patient three days after admission to hospital. *C*. Autopsy specimen of portion of colon showing two perforations.

With the knowledge that there is no pathological change when there are no cells in the bowel discharges, he is in a position to reassure his patients and to restore their confidence. The lessening of fear and of nervous tension will often help to reduce the amount of diarrhea.

Group III

Patients with Acute Amebic Dysentery.

Female, aged 62, stated that about 10 days prior to her examination she had developed some looseness of the bowel for about 5 days and had passed about a teaspoonful of mucus. Her symptoms were quite insignificant, but because she and her husband had lived in Mexico for many years and because her husband had been found to be infected with *Endameba histolytica,* she was given a saline laxative and her stools were examined. All specimens were negative for cells, but motile forms of *Endameba histolytica* were found. (Figure 3B.)

The typical picture of acute amebic dysentery infestation with no cellular exudate was seen in this patient, and it could be stated with confidence that the only involvement of the bowel was that which was related to the presence of *Endameba histolytica.*

Group IV

Acute Amebiasis Complicated by Perforation.

Male, aged 35, chronic alcoholic who complained of diarrhea of six weeks' duration. Blood and mucus were passed with the diarrheal discharges. When first seen the patient was in extremis. The abdomen was distended, tympanic, fever was up to 105°, and there were 31,000 leukocytes. Examination of the stool revealed a moderately heavy cellular exudate, scattered among which were numerous *Endameba histolytica* (figure 5A). The day following the first examination, the patient passed a cast of the bowel (figure 5B) and died 48 hours later. At autopsy, the findings were confluent ulcerations of the entire large intestine and rectum with perforation and generalized fibrinous peritonitis (figure 5C, autopsy specimen).

This case represents that group of amebic dysentery in which complications have arisen through damage to the bowel wall other than that which is caused by the invasion of *Endameba histolytica.* The bowel wall may be damaged by various bacteria, such as the bacillary dysentery group of organisms, by toxic agents, etc. In this patient, stool examination showed not only the presence of *Endameba histolytica* but also evidence of complications in the heavy cellular exudate, which does not ordinarily appear in cases of amebiasis.

Group V

Bacillary Dysentery.

Male, aged 14, had a history of sudden onset of diarrhea in the middle of the night with marked tenesmus and passages from the bowel every few minutes. Examination of freshly passed specimens of the bowel discharges were negative for

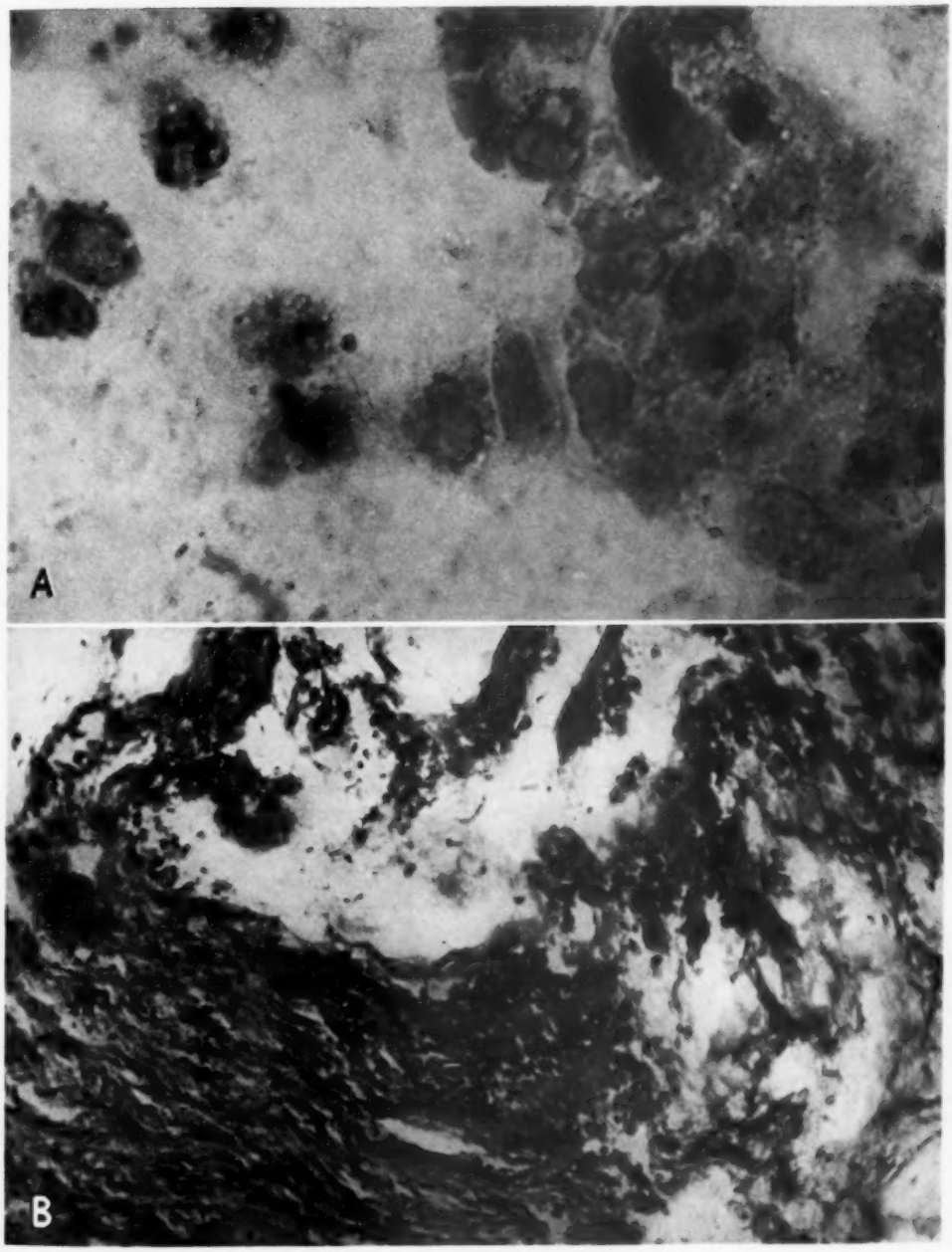

FIG. 6. Carcinoma of the sigmoid colon. *A*. Degenerate epithelial cells in bowel discharges. Loeffler's methylene blue wet preparation: oil immersion. *B*. Section through carcinoma removed at operation.

Endameba histolytica, but showed a heavy cellular exudate typical of bacillary dysentery (figures 2 and 3A). Sigmoidoscopy showed that the bowel mucosa had the usual acute bacillary dysentery appearance. Cultures of the bowel discharges were positive for the Flexner group of organisms. In this case it was possible to culture the bacillary organisms owing to the fact that the onset of the condition was only about 48 hours prior to the time of culture. If the patient has been ill for many days or for weeks, it is not always possible to secure a positive culture.

In these cases the microscopic examination of the stools was important as it gave an indication of the type of pathological condition to be looked for when sigmoidoscopy was performed. The microscopic examination of the stools also gave definite indication of the lines of therapy to be followed.

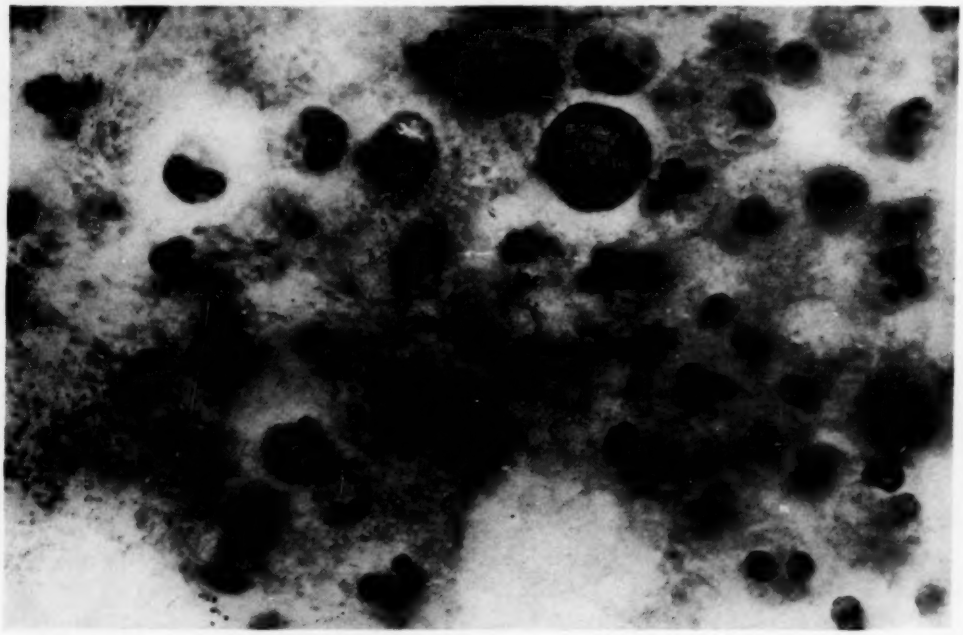

FIG. 7. Cellular exudate from patient with lymphogranuloma venereum of the rectum. Wet fixation in Schaudinn's fluid, Heidenhain's iron hematoxylin counter-stained with eosin; oil immersion.

GROUP VI

Carcinoma of the Sigmoid.

Male, aged 48, referred from Haiti because of diarrhea which had been present for seven months. He passed only four to five stools in the 24 hours, and stated that now there was no blood or mucus present. He had seen blood previously, but his physician had treated him as a case of amebic dysentery owing to the prevalence of that condition in the locality in which he lived. The patient had lost about 23 lbs. in the seven months. He noticed that he did not have good control of his bowel movements. When his symptoms did not respond to antiamebic therapy, he was regarded as a case of "nervous diarrhea," of "sprue," or as a possible infectious type of

colitis which required "disinfection of the intestine." Examination of the bowel discharges was negative for amebae, but showed a heavy cellular exudate of degenerate epithelial cells (figure 6). Sigmoidoscopy showed a carcinoma of the sigmoid (figure 6) which was removed by Dr. R. Franklin Carter.

In this patient, the examination of stools showed the presence of heavy cellular exudates. These findings led to the sigmoidoscopic examinations which revealed the true nature of the pathological conditions from which the patient was suffering. The seriousness of the pathological conditions found in this case indicates the importance of making an immediate examination of the bowel discharge for every patient who complains of diarrhea. If blood and mucus are present, and a preliminary examination of the stools does not reveal the presence of cells, the patient should be given three enemas, following each other without delay, or a colonic irrigation, and the mucus evacuated at the conclusion of this treatment should be collected for examination. If a pathological condition is present, the cells should then be manifest. When cells of any type are found in any of these specimens of bowel discharge, the physician must exhaust every means within his power to discover the true nature of the pathological condition present. There is no other way of relieving suffering and prolonging life.

Group VII

Lymphogranuloma Venereum.

Female, aged 42, referred for diagnosis because of complaint of alternating constipation and diarrhea for about four months, with severe pain in the rectum. This patient was given instillations of warm oil in order to relieve the pain. When she was not constipated she had a definite diarrhea with tenesmus and this was accompanied with the almost constant passage of creamy mucus from the rectum. Examination of the bowel discharges revealed the presence of a heavy cellular exudate (figure 7). At sigmoidoscopy, the mucosa was found to be soft velvety and pale pink for about 3 cm. From that point onward numerous small red masses were found, each one of which was perfectly round. These masses were separated from each other, and in the intervening spaces the bowel mucosa presented a normal appearance. The masses were hard and red, and measured about 3 to 4 mm. in diameter. They did not bleed and did not have ulcerated surfaces. They appeared to line the entire rectum, and became more numerous higher up until at 7 cm. from the anus, the bowel became so narrow that it was impossible to pass the sigmoidoscope further. The Frei test was strongly positive. Since beginning the treatment of the patient with the Frei antigen, the symptoms have begun to recede.

In this case, the heavy cellular exudate which was found to be present gave an indication that pathological changes were taking place. Further investigations helped in the determination of the diagnosis.

Group VIII

Carcinoma of the Splenic Flexure of the Colon.

Female, aged 62, complained of pain in the abdomen and of blood in the bowel discharges. Her symptoms had been present for two months. The abdomen was

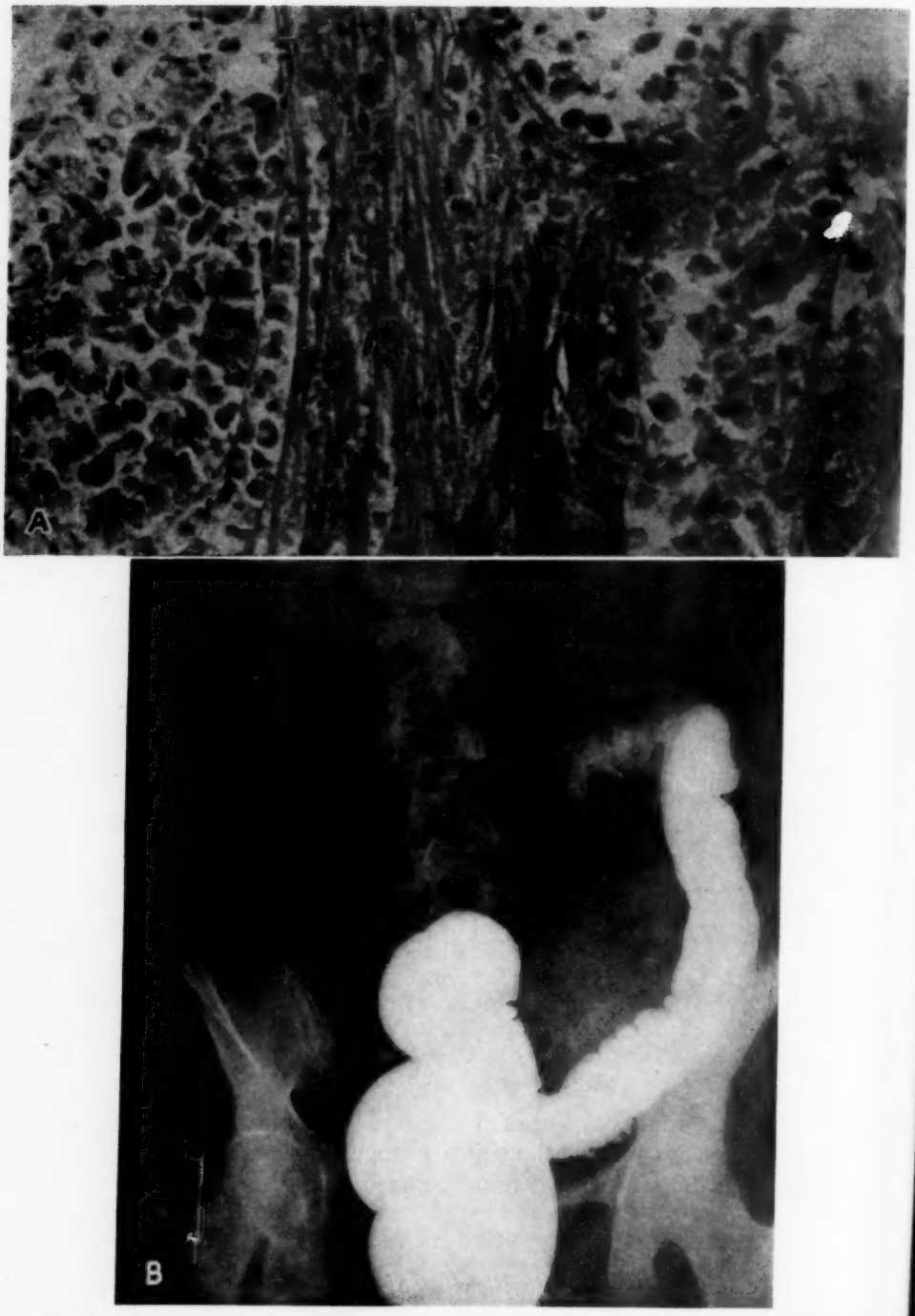

FIG. 8. Carcinoma of the splenic flexure of the colon. *A*. Section through tumor removed at operation. The cells of the bowel discharge were so degenerate that photography was impossible but they appeared similar to those seen in this section. *B*. Barium colon enema roentgenogram.

sore to the touch. She stated that six years previously she had suffered an attack of diarrhea in the course of which she passed as many as 20 bowel movements in the 24 hours. At that time she was told that she was not digesting starches and sugars properly. She also stated that she was now constipated, but that she finally had about three bowel movements daily, through the use of enemas. Without the enemas, she had no bowel movement at all. As a rule there was no result from the first enema, but she developed a sense of pressure in the abdomen and after the second enema the bowels moved. Blood has been present in the bowel movements for about two months. This symptom was coincident with the onset of the abdominal pain for which she was referred. Sigmoidoscopy showed that the bowel mucosa was soft velvety and pale pink, but examination of the mucus aspirated through the sigmoidoscope revealed the presence of a heavy cellular exudate. Roentgen-ray examination with the barium colon enema showed retardation of the barium at the splenic flexure. Laparotomy by Dr. William F. MacFee revealed a large tumor of the splenic flexure of the colon, and the pathological diagnosis was adenocarcinoma of the splenic flexure (figure 8).

Group IX

Pathological Changes of the Terminal Ileum.

Male, aged 54, referred because of the complaint of diarrhea for one year, with an average of five to eight bowel movements every 24 hours. Loss of weight amounted to 45 lbs. in the past six months. The patient stated that there was not at any time any blood present in the diarrhea. Examinations of the freshly passed warm specimens of stools were negative for amebae and also for cellular exudates. The patient was prepared for sigmoidoscopy with tepid normal saline enemas. The examination showed that the mucosa was generally edematous, only moderately inflamed and slightly atrophic. A few submucus hemorrhagic areas were present. Mucus aspirated through the sigmoidoscope showed a heavy cellular exudate, and the conclusion from roentgenological studies was "diffuse inflammatory process involving the coils of the terminal ileum associated with polypoid changes."

Summary and Conclusions

These case histories, which have been summarized briefly, fall into nine typical groups. In all instances, the patients complained of diarrhea. Cellular exudate studies were made in all cases. With the information obtained from these studies, it was possible to determine whether or not the patients had pathological conditions of the bowel mucosa. In view of the extensive investigations into the validity of these cellular exudate studies, a brief description as well as the findings of which have been given, it is demonstrably safe for the physician to act on the principle that when cells are not found in the bowel discharge after exhaustive and painstaking search, there is no pathological change present; but whenever cells are found, their presence indicates that pathological changes are taking place in the bowel mucosa. Further investigation, with the sigmoidoscope and roentgen-ray, if necessary, must be undertaken immediately in order to locate and identify the pathological condition which the presence of cellular exudate in the bowel discharges shows to exist.

The microscopic examination of the bowel discharge for the presence or absence of cellular exudate is therefore the first step to take for diagnosis and for the subsequent treatment of every patient who is suffering from any of the symptoms associated with bowel complaint.

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THE RÔLE OF CORONARY ARTERY DISEASE IN THE ETIOLOGY OF AURICULAR FIBRILLATION *

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THE prevailing views concerning the rôle of coronary artery disease in the etiology of auricular fibrillation appear contradictory. Although its ultimate cause remains obscure, this arrhythmia is known to be associated with certain clinico-pathological states to which a greater or lesser degree of etiological significance is generally ascribed and among which coronary artery disease is frequently included.[1, 2] On the other hand, it is well known that auricular fibrillation and angina pectoris of coronary origin occur together but rarely, and it has been suggested that these two conditions are more or less incompatible.[1, 2, 3] Furthermore, although transient auricular fibrillation develops quite commonly during the early course of acute coronary occlusion, the rarity with which acute coronary thrombosis occurs in cases of established auricular fibrillation has been noted by many observers.[3, 4] It thus appears that with respect to auricular fibrillation, coronary artery disease is regarded at the same time as of both causative and preventive significance. For the purpose of shedding some light upon this apparent paradox the following investigation was carried out.

(*A*) The records of 100 consecutive cases which came to autopsy with a clinical diagnosis of auricular fibrillation were analyzed to determine (1) the underlying pathological lesions, (2) the average age at death, (3) the degree of cardiac decompensation, and (4) the degree of coronary atherosclerosis. The degrees of decompensation and of coronary sclerosis were for convenience graded as 1, 2, 3, and 4, signifying respectively, moderate, moderately severe, severe, and extreme. The results of this analysis which are recorded in table 1 may be summarized as follows:

TABLE I

100 Cases of Auricular Fibrillation

Underlying Pathological Lesion	No. of Cases	Age	Cardiac Decompensation*	Coronary Sclerosis*	Blood Pressure	Heart Weight
Acute coronary occlusion	9	71.5	3.5	3.75	167/101	466
Toxic thyroid	6	66.1	3.25	1.0	156/85	400
Rheumatic endocarditis	23	48.5	3.43	1.05	143/88	600
Luetic aortitis	1	38.0	4.0	—	130/?	700
Others	61	68.7	3.40	2.29	166/104	600
Total or Average	100	63.8	3.42	2.06	161/100	576

* On a scale of 0 to 4.

* Received for publication July 10, 1939.
From the Departments of Medicine and Pathology of the University of Oregon Medical School.

The average age was 63.8 years, the average degree of decompensation was 3.40 or a grade between severe and extreme, and the degree of coronary atherosclerosis was on the average 2.06 or only moderately severe. The only instances of severe to extreme grade of coronary atherosclerosis (3.22) were noted in the group of nine cases of acute coronary thrombosis in which it seemed probable that the arrhythmia appeared for the first time after the acute occlusion.

An examination of the underlying pathological lesions revealed that in 38 of the cases the auricular fibrillation was associated with those clinico-pathological states which are known to have some influence upon the development of this arrhythmia. However, in 61 of the cases the only disturbances found were (1) clinically, a high degree of congestive failure (3.42) with a significantly elevated blood pressure, and (2) pathologically, varying degrees of cardiac enlargement (average weight 576 gm.) with a moderately severe grade of coronary sclerosis (2.29). In addition there was one case of luetic aortitis in which auricular fibrillation developed in association with an extreme degree (grade 4) of cardiac decompensation although the coronary arteries (including their orifices) were entirely free from disease.

(*B*) For comparison, in order to determine whether this moderately severe grade of coronary sclerosis may be viewed as of etiological importance in the genesis of the associated auricular fibrillation, an analysis was made of the records of a second series (table 2) of 100 consecutive cases which came to autopsy with a clinical diagnosis in which the rhythm was stated to be "regular" or "sinus," and in which the average age at death (69.7) approximated that of the 61 cases referred to above (68.7).

TABLE II

100 Cases with Sinus Rhythm

No. of Cases	Average Age	Cardiac Decompensation*	Coronary Sclerosis*	Blood Pressure	Heart Weight
100	69.7	1.13	2.01	146/85	394

* On a scale of 0 to 4.

An examination of the data so obtained and recorded in table 2 shows that the average grade of coronary sclerosis present in the 100 cases with regular or sinus rhythm was 2.01 or but slightly lower than that found in the 61 cases with auricular fibrillation recorded in table 1. On the other hand the grade of congestive failure in the non-fibrillating cases of Series II was only 1.13 or much less than the high degree (3.40) of failure present in the 61 cases with auricular fibrillation of Series I.

Further comparison of the two tables discloses two other important differences. The blood pressure values and heart weights which were within normal limits in non-fibrillating cases (Series II) were found significantly

increased in those with the abnormal rhythm (Series I). The thought, therefore, suggests itself that hypertension, congestive failure and cardiac enlargement rather than coronary sclerosis might be the important factors in the genesis of auricular fibrillation.

(*C*) The records of a third group of 100 consecutive cases were chosen for analysis within the same age group (table 3). In the selection of this

TABLE III

100 Cases Selected to Indicate Relation of Age to Incidence of Coronary Sclerosis

No. of Cases	Average Age	Coronary Sclerosis*
100	67.9	2.46

* On a scale of 0 to 4.

series no attention was paid to the diagnosis or the character of the cardiac rhythm. The information desired in connection with the examination of this third series of records was the influence of "age" upon the incidence of coronary sclerosis independent of the presence or absence of auricular fibrillation. It will be seen from an examination of table 3 that the average grade of coronary sclerosis for this group (average age 67.9) was 2.46 or even slightly higher than that found in the 61 cases with auricular fibrillation belonging to Series I. This observation suggests the thought that the coronary sclerosis noted in the 61 cases of Series I was related to the advanced age rather than to the auricular fibrillation.

(*D*) A fourth series of records of 100 autopsied cases (table 4) was selected for study from approximately the same age group (average age

TABLE IV

100 Cases, Some with Sinus Rhythm and Some with Auricular Fibrillation

Rhythm	No. of Cases	Average Age	Cardiac Decompensation*	Coronary Sclerosis*
Auricular fibrillation	19	71.2	3.16	2.00
Regular	81	70.4	1.09	2.148
Total or Average	100	70.5	1.47	2.122

* On a scale of 0 to 4.

70.5 years). This series of 100 consecutive cases chosen on the basis of age was analyzed with respect to (1) the character of the cardiac rhythm, (2) the degree of coronary sclerosis and (3) the degree of congestive heart failure. In 19 cases auricular fibrillation was noted and in 81 cases the rhythm was reported as having been regular or sinus. As will be seen from an examination of table 4 the degree of coronary sclerosis for the 19 cases with auricular fibrillation was no greater or even a little lower (2.00) than

that recorded for the 81 cases with regular or sinus rhythm (2.148). On the other hand the grade of congestive failure noted in the 19 cases with auricular fibrillation was much higher (3.16) than that observed in the 81 cases with regular or sinus rhythm (1.09).

(*E*) Finally, a fifth series of records was examined for the purpose of confirming the fact now generally recognized that auricular fibrillation occurs but rarely in cases of angina pectoris. This group consists of the records of patients under active treatment for whom there was made a diagnosis of angina pectoris on the basis of coronary artery disease. As will be seen from an examination of table 5, auricular fibrillation was noted in only five cases in all of which a high grade of congestive failure was present. The degree of decompensation noted in the five fibrillating cases was 3.4 compared to a grade 1.3 for the non-fibrillating cases.

TABLE V

100 Cases of Angina Pectoris of Coronary Origin

Rhythm	No. of Cases	Average Age	Cardiac Decompensation*	Blood Pressure
Auricular fibrillation	5	69.0	3.4	135/89
Regular	95	61.0	1.30	158/91
Total or Average	100	61.4	1.41	157/91

* On a scale of 0 to 4.

COMMENT

The results of the foregoing analyses would seem to indicate that coronary sclerosis bears no direct relationship to the development of auricular fibrillation. The degree of sclerosis noted in cases with auricular fibrillation was no greater than that observed in persons of a similar age group in whom the rhythm was " regular " or " sinus." On the other hand a definite relationship was observed between this arrhythmia and congestive failure; the degree of the latter was invariably significantly higher in the cases with auricular fibrillation than in those with regular or sinus rhythm. In this connection it was obviously desirable to determine whether symptoms of decompensation preceded the onset of auricular fibrillation. Unfortunately, such determination was not often possible. However, in the few instances (13 cases) in which information bearing on this point was available, the evidence suggested that symptoms of congestive failure (edema or dyspnea) preceded those of auricular fibrillation (palpitation). In four instances the records clearly indicated that on admission there were signs of congestive failure and regular rhythm with the subsequent development of auricular fibrillation.

The evidence herein presented, therefore, appears to suggest that a probable relationship exists between congestive failure and auricular fibrilla-

tion, but that coronary sclerosis, except insofar as it may be concerned in the production of congestive failure, cannot be regarded as an etiological factor in the genesis of auricular fibrillation. The frequent appearance of transient auricular fibrillation following an attack of acute coronary occlusion may be explained on the basis of an associated congestive failure which, though often in but slight degree, so frequently develops after such an accident. Master, Dack and Jaffe [5] in a study of 300 cases of coronary artery thrombosis noted that the incidence of increased arterial tension, enlarged heart and congestive heart failure was definitely greater among these cases which developed auricular fibrillation than in the control group. It is also noteworthy that in experimental ligation of the coronary arteries in animals, which operation frequently results in various types of cardiac arrhythmias, auricular fibrillation and flutter are rarely encountered.[5, 6]

Although in the various series of cases described above there was not observed a single instance in which auricular fibrillation was noted in the absence of congestive failure, it is, of course, well known that such cases do occur, especially in the presence of mitral stenosis, thyrotoxicosis, or hypertension. The exact mechanism involved in the production of the arrhythmia under such circumstances is not known. However, it is probable, at least in the cases with mitral stenosis, that the stretching of the left auricle is a major factor. This possibility is also applicable to the cases of hypertension where distention of the left auricle due to increased intra-auricular pressure may result in auricular fibrillation even before there is gross evidence of failure of the left ventricle.

If the concept that distention of the left auricle is an important factor in the initiation of auricular fibrillation proves valid it will afford an explanation for the interesting clinical observation that auricular fibrillation is so rare in isolated failure of the right side of the heart arising from pulmonary heart disease [7, 8, 9]; for in this type of congestive heart failure, though the right auricle is often markedly dilated and hypertrophied the left auricle remains normal or even smaller than normal.

The above observations concerning the rôle of coronary artery disease in the etiology of auricular fibrillation are not altogether original. Essentially similar investigations with like results were reported by Cookson [10] in 1930 and Brown [11] in 1935. However, the present effort appears justified by the frequent inclusion of coronary sclerosis among the etiological factors of auricular fibrillation noted in the current literature and in recent textbooks.

The question involved is not solely of academic interest; its practical implications concern both diagnosis and prognosis as illustrated in the following observation.

A woman, 42 years of age, without any signs of antecedent congestive failure, suddenly developed persistent auricular fibrillation. After a period of two months without adequate treatment, severe congestive failure supervened. The electrocardiogram confirmed the presence of auricular fibrillation, but indicated otherwise normal

ventricular complexes. Because of the high degree of congestive failure, and since a careful investigation excluded hyperthyroidism and rheumatic or hypertensive heart disease, a diagnosis of coronary artery disease as the underlying etiological factor received serious consideration and an unfavorable prognosis was implied. However, under proper management including adequate digitalization the signs of congestive failure rapidly disappeared, and normal rhythm was readily restored by means of quinidine. Rapid and complete recovery ensued with resumption of normal activity without further treatment. Three years later the patient continues to enjoy perfect health.

In the light of the observations recorded in this communication coronary artery disease might well have been excluded from consideration in the above-described case in favor of a diagnosis of "functional auricular fibrillation" with a favorable prognosis now fully justified by subsequent developments.

Summary and Conclusions

A. Data obtained from an examination of the records of 400 autopsied cases tend to suggest that:

1. In the absence of congestive heart failure or acute coronary occlusion, coronary artery disease is not a cause of auricular fibrillation.
2. Congestive heart failure involving the left side of the heart, regardless of the underlying pathological lesion, tends to favor the development of auricular fibrillation. It is suggested that stretching of the left auricle might be an important factor in this process.*
3. Coronary artery disease, although not a direct cause of auricular fibrillation, nevertheless may be concerned indirectly in the genesis of the arrhythmia by first inducing congestive failure. This mechanism is offered as a probable explanation for the frequent appearance of transient auricular fibrillation following an attack of acute coronary thrombosis, although this arrhythmia occurs very rarely in angina pectoris of coronary origin prior to the onset of congestive failure.
4. In a case already in congestive failure, the subsequent appearance of auricular fibrillation affords no additional information which might serve as an aid in determining the presence or the absence of coronary artery disease.

B. An analysis of the records of 100 cases of angina pectoris under active treatment confirms the observation already noted by many authors that auricular fibrillation is rare in angina pectoris of coronary origin, except in the presence of congestive failure.

* The effect of failure of the left ventricle upon the left auricle is often indicated by changes in the electrocardiogram relating to auricular activity, which are strikingly similar to those occurring in mitral stenosis. These changes which are believed to be due to hypertrophy and dilatation of the left auricle consist of a widened P-wave of low voltage, usually bifid or flat-topped. They have been recently described by Wood and Selzer [12] as a new and *early* sign of left ventricular failure.

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THE BALANCE BETWEEN CAPSULAR POLYSACCHARIDE AND ANTIBODY IN RELATION TO THE PROGNOSIS AND THERAPY OF PNEUMOCOCCAL PNEUMONIA *

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INTRODUCTION

THE antigen-antibody balance in pneumococcal pneumonia was first reported by Blake,[1] who employed the methods of detection described by Dochez and Avery.[2, 3] Blake[1] studied 19 cases and demonstrated capsular polysaccharide in the blood of 11, 10 of whom died. Circulating antibody was not detected in these patients, nor in those who excreted large amounts of capsular polysaccharide in the urine. It has since been shown experimentally that capsular polysaccharide may interfere with defenses against the pneumococcus by enhancing the invasive power of pneumococci (Felton and Bailey[4]; A. W. Downie[5]), or by blocking the reaction between pneumococcal antigen and homologous antibody (Felton and Bailey,[4] Sickles[6]).

Although the therapeutic value of specific serum in pneumococcal pneumonia has been well established,[7, 8, 9, 10, 11, 12] its effectiveness in the presence of capsular polysaccharide has not been investigated. The introduction of sulfapyridine provided an additional impulse to make further correlations between the immunological responses in pneumonia and recovery. Our particular interest was directed towards noting the comparative influence of sulfapyridine, specific serum, or the combination, on the antigen-antibody balance, and its relation to the outcome of therapy. In a previous communication[13] we briefly summarized the results of our studies of 25 cases, describing two cases, and recording observations suggesting that sulfapyridine alone may be ineffective in the presence of free circulating capsular polysaccharide. It is the purpose of this report to analyze the 25 cases, to add our later observations on one (W. L.), and on a twenty-sixth case observed during the course of the analysis.†

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† During the course of analysis of this series, an additional case of pneumococcus type III pneumonia, bacteremic, in whose blood capsular polysaccharide was detected, came under observation. This patient, treated with sulfapyridine alone, recovered after a stormy course, capsular polysaccharide continuing to be detectable in the blood for a period of 10 weeks, throughout which time the urine repeatedly contained capsular polysaccharide. During the greater part of her hospital stay, there was roentgenological evidence of a collection of air and fluid in the pleural space of the affected side. This effusion subsided spontaneously, the

METHODS

Since January, 1939, the treatment of pneumonia patients at Harlem Hospital (Pneumonia Service), has been rotated, according to type, to provide the following three series: (1) antipneumococcal serum alone, (2) sulfapyridine alone, (3) antipneumococcal serum and sulfapyridine. On admission, sputum was obtained for immediate typing and a blood culture was taken. As soon as the type was available, the patient was treated according to the group into which he fell. For each antigen-antibody determination, the serum obtained from 15 c.c. of clotted blood was subjected to study within a week of removal. Sera were always refrigerated, without preservative, in corked tubes, until used. Blood cultures were repeated frequently.

(*a*) *Antigen* (*capsular polysaccharide*) *detection:** Half c.c. quantities of serial dilutions of patient's serum (employing 0.85 per cent saline as diluent) were mixed with 0.5 c.c. of a water-clear 1/10 dilution of homologous rabbit antipneumococcal serum, having an original antibody titer of 5,000 to 10,000 units per c.c. Final dilutions of patient's serum obtained were 1 to 2; 1 to 4; 1 to 8; and 1 to 16. (*b*) *Precipitin detection:* Half c.c. of the "optimal" saline dilution (previously determined for each type) of capsular polysaccharide, prepared from stock saline solutions of 1–1,000 or 1–5,000 concentration, were mixed with 0.5 c.c. of serially diluted patient's serum. Final dilutions of patient's serum were also 1 to 2; 1 to 4; 1 to 8; and 1 to 16. (*c*) *Agglutinin detection:* Half c.c. of saline suspensions of the sediment from 18 hour broth cultures, giving an evident specific Neufeld reaction, were mixed with 0.5 c.c. serial dilutions of patient's serum; dilutions were carried to 1 to 64. (*d*) *Controls:* These consisted of half c.c. of patient's serum with (1) 0.5 c.c. of heterologous antipneumococcal rabbit serum and (2) 0.5 c.c. of heterologous polysaccharide (in appropriate dilution), (3) half c.c. of homologous antipneumococcal rabbit serum plus half c.c. of homologous polysaccharide; (4) half c.c. of homologous antipneumococcal rabbit serum plus half c.c. of heterologous polysaccharide; (5) 0.5 c.c. of suspension of organisms plus 0.5 c.c. of saline; (6) 0.5 c.c. of homologous antipneumococcal rabbit serum plus 0.5 c.c. of saline; (7) 0.5 c.c. of homologous capsular polysaccharide plus 0.5 c.c. of saline.

All mixtures were made in 10 by 75 mm. precipitation tubes. The tubes were placed in the water bath at 37° C. for 2 hours, and then refrigerated overnight. Reactions were read after the period of refrigeration.†

Positive precipitative reactions varied from a fine cloud to a granular precipitate. An occasional "button" type of precipitate was observed.[14] Controls, both positive and negative, were always in order.

Sulfapyridine Therapy: The initial dose of sulfapyridine was 5 grams, followed by 1 gram 4-hourly, day and night until the temperature had been normal or below 100° F. for three consecutive days. In some instances treatment was continued for as long as 10 days and occasionally given in several courses. Blood for sulfapyridine concentration was obtained on the morning following commencement of treatment,

patient remaining afebrile during the last several weeks. The patient was discharged from the hospital 10 weeks ago, has been followed at regular intervals and is still clinically well. Her blood and urine have been negative for capsular polysaccharide for at least six weeks. This case will be included in the numerical analysis which follows.

*The methods of detection employed for these 26 cases are those originally used by Dochez and Avery and by Blake. Further observations in our laboratories indicate that the sensitivity of detection of capsular polysaccharide can be increased by mixing equal quantities of undiluted patient's serum with the "optimal" dilution of type-specific antibody solution. These "optimal" dilutions have been determined for the different pneumococcal types studied.

†We have been able to increase the rapidity and sensitivity of all the reactions by employing high-speed centrifugation instead of the usual procedure.[14, 15]

and at 48-hour intervals thereafter. Sulfapyridine concentrations were determined with an optically balanced two-celled, photoelectric colorimeter.

Serum Therapy: Either horse or rabbit sera or both were employed in therapy, rabbit serum having been used in most cases. The majority of patients received between 100,000 and 300,000 units of serum, administered at 2-hourly intervals, intravenously, the usual precautions in testing for sensitivity having been observed. Where bacteremia was discovered or clinical response to the initial dosage of serum was inadequate, additional serum was usually given, the duration of therapy extending, in these cases, to as long as 52 hours.

Serum and Sulfapyridine: Sulfapyridine and antipneumococcal serum, when combined, were used in the same dose employed for those receiving either alone.

Results

The 26 cases were distributed among the following types: I, 8 cases; II, 1 case; III, 8 cases; IV, 1 case; VII, 8 cases. The type was obtained from the sputum in all cases; in 10 patients bacteremia was present. The sera from 16 patients were studied before and after initiation of therapy, while examination of the sera from the remaining 10 was begun immediately after the commencement of therapy.

One hundred and thirty-five series of determinations were carried out in all. Generally, bloods were obtained at daily intervals, immediately after beginning of therapy, until temperature fell to normal or the patient died. The frequency of subsequent determinations varied with the clinical response of the patient, these being at shorter intervals (1 to 3 days) where the response was poor, and at longer intervals where the control of infection was rapidly effective.

(A) *Treatment with Sulfapyridine Alone:* Table 1 summarizes the results obtained in 12 cases treated with sulfapyridine alone. In three cases capsular polysaccharide was detectable in the blood; all were pneumococcus III bacteremias, one with an empyema on admission. Two of these patients died despite attainment of a 2 to 6 mg. per 100 c.c. concentration of sulfapyridine in the blood. The third, as previously mentioned, is apparently well. Antibodies became detectable in the blood of 9 of these 12 patients; agglutinins in all 9, and agglutinins and precipitins in only three.

Of the three patients who failed to develop demonstrable antibodies, two recovered. One of these patients was a pneumococcus I bacteremia, the other an uncomplicated pneumococcus III without bacteremia. Neither of these patients had capsular polysaccharide in the blood.

The third patient, referred to in an earlier communication,[11] was a 69-year old negro male, admitted on the fifth day of disease with a pneumococcus III bacteremia. The serum of this patient gave a positive reaction for capsular polysaccharide and he died on the seventh day of disease, despite a blood sulfapyridine concentration of 5.4 and 4.7 milligrams per cent on the sixth and seventh days. Antibody did not develop and there was no appreciable decrease of circulating polysaccharide, although the number of colonies from the blood culture had progressively decreased.

Of the remaining nine patients in whose blood antibodies became de-

TABLE I

Sulfapyridine

Type	Patient	Age (yrs.)	Treatment		Sulfapyridine Concentration in Blood Milligrams %	Serum Titer ‡		
			Day of Disease when Started	Quantity Grams		Capsular Polysaccharide	Agglutinins	Precipitins
I	119776	12	6th	57	4.8 4.0 3.6	Negative	1:32	1:16
I*	116356	23	6th	39	5.4 5.3	Negative	Negative	Negative
I	115471	27	6th	48	5.1 5.0 5.0 4.3	Negative	1:8	Negative
III	115516	28	9th	26	5.4 6.0	Negative	1:4	Negative
III	116114	39	4th	50	7.4 6.6 5.4 8.6	Negative	1:32	Negative
III	115451	42	3d	34	4.5 3.3 2.6	Negative	Negative	Negative
VII	118813	36	9th	30	4.8 2.4 1.4	Negative	1:64	1:8

* Bacteremia. † Died. ‡ Highest Titer.

TABLE I—*Continued*

Type	Patient	Age (yrs.)	Treatment		Sulfapyridine Concentration in Blood Milligrams %	Serum Titer ‡		
			Day of Disease when Started	Quantity Grams		Capsular Polysaccharide	Agglutinins	Precipitins
VII	116359	55	3d	57	5.4 7.4 6.4 8.0	Negative	1:4	Negative
VII	121215	62	4th	28	5.9 4.8 14.8	Negative	1:16	1:8
III*	122085	45	8th	108	8.0 10.2 4.4 7.6 7.8 9.8 2.6 9.0 12.6	Positive	1:2	Negative
III*	114515†	54	?	16½	4.3 1.8	Positive	1:32	Negative
III*	116164†	69	5th	21	5.4 4.7	Positive	Negative	Negative

tectable, six developed only agglutinins. Five of these patients recovered, one of whom had capsular polysaccharide in the blood, and bacteremia. Two of the recovered patients developed detectable antibodies prior to clinical recovery, while the remaining three patients developed antibodies after clinical recovery. In the urine of three of these patients, all pneumococcus III, capsular polysaccharide had been detectable at the time of febrile elevation. The urine of others was not studied.

The sixth patient in this group died. Capsular polysaccharide was detectable in her blood prior to commencement of therapy. She was a 54-year old female Puerto Rican. Eight weeks before admission to Harlem Hospital, she had been hospitalized elsewhere for a pneumococcal III, right upper lobe pneumonia, non-bacteremic, complicated by diabetes mellitus and moderate ketosis. With neither sulfapyridine nor specific antipneumococcal therapy, she had made an apparent recovery and had been discharged, although there had been evidence of unresolved fluid at the right base at the time. The diabetes had been controlled with some difficulty. For several weeks following discharge, she had been apparently well, but two weeks prior to admission to Harlem Hospital had developed low-grade fever, with chills and generalized aches and pains. On admission she was acutely ill, hyperglycemic, there was a purulent effusion at the right base, and bacteremia, pneumococcus III (45 col. per c.c.). At this time agglutinins were present (1 to 32) and simultaneously capsular polysaccharide. She was promptly given sulfapyridine, but, because of vomiting, received only 16.5 grams in three days. The blood culture became sterile and temperature fell to normal, though the pulse was slightly elevated. At this point sulfapyridine was stopped. Following a thoracotomy which drained poorly, her temperature rose, ketosis progressed, she developed stupor and died on the eighth day of hospitalization, 48 hours after cessation of sulfapyridine.

The last three patients developed detectable precipitins as well as agglutinins; there was no detectable capsular polysaccharide in their blood. All three of these patients recovered. In one of these patients withdrawal of sulfapyridine was followed by temporary elevation of temperature and diminution of precipitin titer. This was followed, in 36 hours, by spontaneous return of normal temperature, increasing antibody titer, and clinical recovery. The observation suggests that some of the febrile reactions which follow withdrawal of sulfonamide compounds represent abortive reinfections due to a short reactivity of residual, unkilled organisms. During this reactivity such organism growth may be productive of enough capsular polysaccharide to neutralize precipitin without itself becoming detectable. In this same patient, pneumococcus VII, X and XVI were found in the sputum. Capsular polysaccharide for type VII alone was detected in his urine. That this was the infecting type was confirmed by the detection, on several occasions, of a type VII precipitin in his blood.

(B) *Treatment with Serum Alone:* Table 2 summarizes the results obtained in eight cases treated with serum alone. In one case capsular polysaccharide was detectable in the blood, a pneumococcus III pneumonia, non-bacteremic. This patient died.

He was a 35-year old negro male admitted on the first day of a single-lobe pneu-

TABLE II
Serum

Type	Patient	Age (yrs.)	Treatment		Serum Titer ‡		
			Day of Disease when Started	Quantity Units	Capsular Polysaccharide	Agglutinins	Precipitins
I*	115803	13	5th	480,000	Negative	1:32	1:16
I	115915	15	7th	160,000	Negative	1:64	1:16
I	116299	37	4th	160,000	Negative	1:64	1:8
II*	117859	60	8th	1,239,000	Negative	1:32	1:16
VII	116181	28	2nd	320,000§	Negative	1:64	1:16
VII*	115698	32	3rd	465,000	Negative	1:32	1:8
IV*	115417†	43	4th	733,000	Negative	Negative	1:16
III	115330†	35	1st	700,000	Positive	1:16	1:4

* Bacteremia. † Died. ‡ Highest Titer. § Horse serum (all others rabbit serum).

monia, pneumococcus III. There was a loud diastolic murmur at the second intercostal space to left of the sternum, and roentgen-ray evidence of marked widening of the ascending aorta, interpreted as syphilitic aortitis with aneurysmal bulge. There was also left ventricular enlargement, and consolidation of the inner portion of the left lung. He was promptly given 700,000 units of type III antipneumococcal rabbit serum. Blood from this patient prior to treatment was negative for both capsular polysaccharide and antibody. On the day following serum therapy, both capsular polysaccharide and agglutinins became detectable and the urine was positive for capsular polysaccharide. On the following day, capsular polysaccharide was no longer detectable, and the antibody titer increased, precipitins appearing as well. Despite the excess of antibody and the disappearance of polysaccharide, he developed a marked tachycardia and persistent fever and died on the fourth day after admission. Postmortem examination by Dr. Solomon Weintraub revealed bilateral lower lobe pneumonia (gray hepatization) with pulmonary edema, syphilitic aortitis and fatty degeneration of the liver. It is difficult to understand why this patient developed detectable polysaccharide only after intravenous serum therapy. The amount detectable in his blood could not have been introduced with the therapeutic serum. It is noteworthy that this patient died despite rapid neutralization of circulating capsular polysaccharide, indication of the severity of infections accompanied by appearance of capsular polysaccharide in the blood stream.

Of the other seven patients, none had capsular polysaccharide detectable in the blood. Six recovered and one patient died. Of the six recovered patients, three were bacteremic. All six had both agglutinins and precipitins in high titer, always detectable in the first blood obtained after injection of the serum. The remaining patient was a pneumococcus IV bacterial endocarditis terminating in a meningitis. Neither capsular polysaccharide nor agglutinins were detectable in the blood, while precipitin was present in relatively high titer at the same time that the blood culture was positive.

(C) *Treatment with Serum and Sulfapyridine:* Table 3 summarizes the

TABLE III

Sulfapyridine Plus Serum

Type	Patient	Age (yrs.)	Treatment				Sulfapyridine Concentration in Blood Milligrams %	Serum Titer ‡		
			Serum		Sulfapyridine					
			Day of Disease when Started	Quantity Units	Day of Disease when Started	Quantity Grams		Capsular Poly-saccharide	Agglutinins	Precipitins
I	116433	37	6th	160,000§	6th	33	6.6 28.4	Negative	1:64	1:8
I	116187	45	3d	110,000§	3d	53	3.9 7.0 7.8	Negative	1:64	1:8
III	115518	46	2d	300,000	2d	23	3.9 8.9	Negative	1:32	1:4
VII	116551	22	7th	232,500	7th	22	3.2 3.6	Negative	Note: Antibodies negative before treatment. No studies made after treatment	
VII*	115898†	47	12th	160,000	12th	29	24.2 6.6 6.0	Negative	1:64	1:16
VII*	112875† (W.L.)	61	3d	2,525,000¶ (in three courses)	12th	242 (in three courses)	1st course 4.0 to 9.3 2d course 9.6 to 12.4 3d course 2.1 to 11.6	Positive	1:64	1:16

* Bacteremia. † Died. ‡ Highest titer. § Horse serum (all others rabbit serum). ¶ Horse and rabbit serum.

results obtained in six cases treated with serum and sulfapyridine. In one of these cases capsular polysaccharide was detectable in the blood. This patient, W. L., described in a previous communication [13] as having recovered with combined therapy, subsequently died.

He was a 61-year old colored male with a severe pneumococcus VII pneumonia who developed an overwhelming bacteremia, despite antipneumococcal serum therapy. He had undergone apparent remission under further serum therapy, combined with sulfapyridine. His blood had then given a positive reaction for capsular polysaccharide, persisting for eight days, together with detectable homologous precipitin. Capsular polysaccharide had finally disappeared, as infection came under control. Following withdrawal of sulfapyridine, the elevation of temperature had recurred and capsular polysaccharide reappeared in the blood, together with detectable antibody. A second course of sulfapyridine, this time without serum, had promptly brought the temperature to normal and capsular polysaccharide had again disappeared from the blood.

The patient remained subjectively well without elevation of temperature or pulse for about two weeks following the second withdrawal of sulfapyridine. This was followed by gradual elevation of temperature to 101° F. Though there had been previous slight loss of antibody from the blood, capsular polysaccharide reappeared only after several days of elevated temperature. At this time the patient developed signs of meningeal irritation, a right lower motor neuron facial paralysis, right hemiparesis, and aphasia. The blood culture was again positive for pneumococcus VII. The cerebrospinal fluid contained numerous polymorphonuclear leukocytes but did not become positive for pneumococcus VII until the following day. He was promptly treated by careful administration of 700,000 units of antipneumococcal serum, and sulfapyridine again. Within four days the temperature had fallen to normal, blood and spinal fluid had become sterile, capsular polysaccharide had disappeared from the blood stream, and he had developed a high titer of circulating precipitins and agglutinins. During the next few days, his temperature remained normal and the meningeal and focal neurologic signs diminished in intensity. However, one week later, the temperature gradually rose again and the spinal fluid culture became positive and remained so, despite maintenance of a concentration of sulfapyridine in both the blood and spinal fluid in the neighborhood of 10 mg. per cent. The blood culture remained sterile, circulating capsular polysaccharide did not reappear, and the circulating antibody titer also remained high. However, the temperature continued to rise, he sank into a stupor, and finally died on the seventy-sixth day of hospitalization. Permission for postmortem examination was withheld.

The organism recovered from his spinal fluid at the time of his terminal escape from sulfapyridine therapy was studied by Dr. Edwin E. Osgood. It was found to be less susceptible to bacteriostasis by sulfapyridine than the first strain, isolated from the same patient earlier in his disease.

Capsular polysaccharide was not detectable in the blood of the remaining five patients. One of these, suffering from pneumococcus VII bacteremia, treated on the twelfth day of disease, died despite a high antibody titer, high sulfapyridine concentration, and sterilization of the blood. Postmortem examination revealed pneumonic consolidation of the left lower and right middle lobes. The four remaining patients recovered. Three of them had a high titer of agglutinins and precipitins immediately after serum therapy, and made uneventful recoveries. In the fourth recovered patient, where

both pneumococcus I and pneumococcus VII were present in the sputum, the blood was negative for antigen and antibody for both types; studies were not made after serum therapy.

Comment

Including the present series, there have now been a total of 16 reported cases of pneumococcal pneumonia in whose blood free capsular polysaccharide was detected.[1, 2, 3] Fourteen of these 16 cases died, a mortality of 87.5 per cent. The blood of one of the survivors contained only traces of polysaccharide.[1] The pneumonias in four of our patients were due to pneumococcus type III, three with bacteremia and the fifth was due to pneumococcus VII also with bacteremia.

Among our cases there were 10 bacteremic patients, of whom four presented detectable circulating capsular polysaccharide simultaneously with the bacteremia. Two of these four patients lived long enough to permit repeated blood determinations. Capsular polysaccharide continued to be detectable in the blood for 8 days and 10 weeks respectively, following the disappearance of bacteria. Three of these four patients died. Two patients had received sulfapyridine alone and one serum and sulfapyridine. Of the six bacteremic patients in whose blood capsular polysaccharide was not detected, two died; one received serum and sulfapyridine and one serum alone. While these observations are in a series too small to be statistically significant, they nevertheless suggest that the occurrence of free polysaccharide in the blood stream implies a more serious prognosis than does bacteremia alone, and that sulfapyridine alone, or even with specific serum, may not cure such patients. However, one patient with capsular polysaccharide in the blood fell in the drug series and recovered under sulfapyridine therapy alone but after a stormy, protracted illness. Reasoning that capsular polysaccharide exerts its effect by the inhibition of defenses against the pneumococcus,[4, 5, 6] we suggest that attempts should be made to "neutralize" capsular polysaccharide by the administration of antipneumococcal serum to those patients in whose blood the substance is circulating. Judging from our experience with W. L. it is suggested that we might have shortened the illness in our recovered patient had specific antipneumococcal serum been administered early in addition to sulfapyridine.

It is possible to determine the presence or absence of capsular polysaccharide in the serum within 1 hour of withdrawal of the blood by the use of the centrifuge,[14, 15] which is at least 12 to 20 hours earlier than it is possible to detect bacteremia. Consequently, if capsular polysaccharide determinations are routinely made it will be possible to select cases with a serious prognosis much more quickly than has been possible heretofore. Accordingly, since it is our belief that such patients should receive optimum therapy as quickly as possible, specific antipneumococcal serum therapy as well as sulfapyridine therapy may be promptly instituted. It remains for further

observations to determine whether or not a greater reduction in mortality of pneumococcal pneumonias, or other pneumococcal infections, may be accomplished by the inclusion of this laboratory criterion as a guide to therapy.

Since capsular polysaccharide continued to be detected in the blood of our recovering patient, it would seem that the polysaccharide may not be toxic per se. The adverse effects of polysaccharide in human infections are probably dependent upon the simultaneous presence of multiplying pneumococci.[4, 5, 6]

Observations on the antibody response of this series of patients under the various forms of therapy, where capsular polysaccharide is not present in the blood, seem less significant. In a certain number of our patients treated with sulfapyridine alone, cure was effected some time before antibody was detected. Finland, Spring and Lowell [16] have also observed a number of cases of type III pneumonia which recovered although after treatment with sulfapyridine was discontinued, there was no evidence of the presence of type specific antibodies in the blood. Robertson, Graeser, Coggeshall and Harrison [17] have presented an excellent review of the literature and additional observations on the recovery of untreated pneumococcal pneumonia patients in whose blood antibodies were not detected.

Summary and Conclusions

1. Repeated simultaneous determinations of capsular polysaccharide and type-specific antibody were made in the blood of 26 patients treated for pneumococcal lobar pneumonia. Twelve patients received only sulfapyridine; eight patients only serum; and six patients sulfapyridine and serum.

2. Free capsular polysaccharide was detected in the blood of five patients, four of whom died. In the one patient treated with serum and sulfapyridine, (W. L.), temporary remission of the disease occurred. He subsequently died from a meningitis, at which stage the pneumococcus isolated from his spinal fluid proved to be relatively resistant to sulfapyridine. One patient, treated with sulfapyridine alone, recovered after a protracted illness requiring several courses of the drug.

3. Ten of the 26 patients were bacteremic. In four of these capsular polysaccharide was detected in the blood; three of these patients died. In six, capsular polysaccharide was not detected; two of these patients died. Bacteremia plus circulating capsular polysaccharide apparently confers a more serious prognosis than does bacteremia alone. It is suggested, on clinical as well as experimental grounds, that, to shorten the illness and decrease mortality of such cases, both antipneumococcal serum and sulfapyridine be employed as the therapy of choice.

4. Capsular polysaccharide can be detected in the blood stream 12 to 20 hours earlier than bacteremia and can be routinely used as a criterion for prognosis and therapy.

5. Of the 21 patients without capsular polysaccharide in the blood, two died; one had a pneumococcus IV endocarditis and meningitis and had been

treated with serum. The other suffering from a single-lobed, pneumococcus VII pneumonia with bacteremia, treated on the twelfth day of disease, with sulfapyridine and serum, died though there was considerable antibody and an adequate sulfapyridine concentration in the blood.

6. Observations in one case suggest that, in some instances, recrudescenses of fever following withdrawal of sulfapyridine are related to transient reinfections.

7. In one case, where three different types of pneumococci were present in the sputum, the infecting type was determined by detecting the specific soluble substance for this type alone in the patient's urine.

8. In only a majority of the recovered patients, who received sulfapyridine alone, were antibodies detected by precipitation or agglutination. Several patients recovered without antibodies in the blood and others died despite the presence of a high titer of antibodies (some of them with sulfapyridine concentrations in the blood between 2 and 6 mg. per cent).

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OBSERVATIONS ON THE ABSORPTION, EXCRETION AND DISTRIBUTION OF SULFANILAMIDE, SULFAPYRIDINE, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE *

By Elias Strauss, Francis C. Lowell, F. H. Laskey Taylor and Maxwell Finland, F.A.C.P., *Boston, Massachusetts*

In a previous paper,[1] Taylor and his associates reported the results of studies on the absorption and excretion of sulfanilamide and sulfapyridine after administration of a single dose by various routes. Special consideration was given in that paper to a glucose-sulfapyridine solution which was shown to be absorbed, excreted and distributed in the body in a manner radically different from that of either sulfapyridine or sulfanilamide. The present paper deals with a continuation of these studies with particular reference to sulfathiazole and sulfamethylthiazole. We include also the results of studies of (*1*) the absorption and urinary excretion of the sodium salts and acetyl derivatives after oral administration, and of the various compounds and their sodium salts after rectal administration, and (*2*) the concentrations of sulfanilamide, sulfapyridine and sulfathiazole in the body fluids and organs of patients who died during treatment with these drugs.

Materials and Methods

The subjects were all adult males. Three were normal volunteers and the others were ward patients, most of whom were convalescing from mild infections. None had received sulfonamide therapy within a week of the time these studies were begun. Blood non-protein nitrogen and urinary phenolsulfonphthalein excretion were normal in each instance. The ages and weights are given in table 1. Some of the studies on the distribution of drugs between plasma and red blood cells were made on blood taken from patients under treatment for various infectious diseases.

During the studies on absorption and excretion, the subjects were on a regular "house" diet with a fluid intake maintained at 3 liters a day. A uniform dose of 5.0 grams was used in each experiment. The intravenous injections were all given in 500 ml. of physiological saline over a period of 1 hour. The subcutaneous injections were given in a liter of fluid over a period of 1½ hours; the sulfanilamide was given in saline and the sulfathiazole was prepared by adding the 5 grams of powdered drug to a liter of

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We are indebted to Elizabeth Shaler Smith, Louise Sheldon and Margaret A. Adams for technical assistance in carrying out the chemical determinations.

TABLE I

TABLE I

Maximum Blood and Urine Concentrations and Urinary Excretion of Sulfanilamide Compounds after Intravenous, Subcutaneous and Oral Administration of a Single 5-gram Dose

Compound	Subject			Maximum Blood Concentration			Maximum Urine Concentration				Urinary Excretion			
											Per Cent of Administered Drug Recovered*		Per Cent of Recovered Drug Conjugated	
	No.	Age	Weight (kg.)	Hours After Administration	Mg. Per Cent		Period (hours after administration)	Volume (ml.)	Mg. Per Cent		In 24 Hours	In 72 Hours	First 24 Hours	24–72 Hours
					Free	Total			Free	Total				
After Intravenous Injection														
Sulfanilamide	1	43	69	0	11.7	13.4	1–2	430	56	70	46.9	84.2	38.5	76.0
	2	39	70	0	11.1	11.1	1–2	310	124	174	75.6	93.7	42.6	66.2
Sodium sulfapyridine	1			0	9.5	10.3	12–24	780	24	179	61.4	90.0	74.9	90.1
	3	63	68	0	9.8	11.1	2–5	300	116	202	84.5	99.7	61.6	84.1
	4	26	58	0	9.9	9.9	0–2	25	215	332	37.7	80.0	22.0	37.0
Sodium sulfathiazole	5	64	66	0	14.5	14.5	2–5	75	263	332	67.2	80.3	30.6	40.0
	6	31	94	0	12.0	12.1	1–2	275	224	242	85.7	91.0	12.0	24.6
	7	45	69	½†	12.5	12.7	1–2½	90	440	445	79.0	84.0	11.0	34.4
Sodium sulfamethylthiazole	8	24	58	½†	9.8	10.1	½–2	40	146	146	50.3	62.0	16.0	46.9
	8			¾†	9.7	10.0	¾–1	110	154	154	48.0	60.5	8.5	38.6
	9	58	89	0	12.4	12.5	6–12	600	97	113	51.8	60.1	12.0	44.0
After Subcutaneous Injection														
Sulfanilamide	1			4½	9.0	10.6	12–24	1160	44	110	61.6	99.2	47.0	67.4
	2			4½	7.1	8.0	12–24	1700	42	94	68.4	92.5	43.6	69.7
Sulfathiazole*	8			1	6.9	6.9	1–2	50	523	529	73.1	76.0	2.4	25.3
	7			1	6.4	6.5	2–5	100	827	827	82.6	89.3	3.6	21.0

* For the sodium salts, the urinary excretion is corrected both for sodium and for water of crystallization.
† First blood sample.

TABLE I—*Continued*

Compound	Subject			Maximum Blood Concentration			Maximum Urine Concentration				Urinary Excretion			
					Mg. Per Cent				Mg. Per Cent		Per Cent of Administered Drug Recovered*		Per Cent of Recovered Drug Conjugated	
	No.	Age	Weight (kg.)	Hours After Administration	Free	Total	Period (hours after administration)	Volume (ml.)	Free	Total	In 24 Hours	In 72 Hours	First 24 Hours	24–72 Hours
After Oral Administration														
Sulfanilamide	1			5†	6.6	7.8	12–24	1050	39	99	50.3	78.6	46.8	71.8
	2			5†	4.9	6.5	6–12	1180	51	84	71.8	90.7	43.7	67.0
Sulfapyridine	1			5†	3.2	5.3	12–24	700	21	153	47.0	76.0	76.0	83.0
	2			5†	5.5	7.7	6–12	1190	45	118	78.0	93.0	67.0	88.5
	4			5†	5.7	7.0	6–12	1100	45	67	47.2	82.8	24.4	44.0
Sodium sulfapyridine	5			2	7.9	8.5	12–24	250	125	200	29.0	70.1	27.0	49.7
	9			3	5.9	6.4	3–8	350	82	97	36.5	71.2	19.3	49.2
	10	35	65	6	5.7	6.4	6–12	700	73	99	46.0	—	24.0	—
Sulfathiazole	6			2	7.3	7.8	2–3	275	224	242	77.0	85.0	15.0	15.4
	5			6	8.8	10.3	12–24	530	187	250	66.6	90.0	19.0	33.5
	6			3	7.2	7.6	3–6	320	256	256	60.0	73.0	9.0	6.2
	7			3	9.5	10.4	2–3	100	322	339	65.0	80.0	4.0	60.0
Sodium sulfathiazole	7			2	9.4	9.9	2–3	150	240	247	64.3	73.0	6.3	44.4
	9			3	7.9	8.3	6–12	400	149	152	42.0	49.0	5.0	27.3
	11	27	61	3	8.1	8.2	1–3	35	406	455	66.0	72.0	7.0	26.0
Sulfamethylthiazole	9			3	4.8	4.8	3–12	1000	65	82	22.9	34.3	24.0	44.5
	12	27	59	4	5.5	6.0	4–6	50	131	186	25.6	38.0	35.0	54.1
	13	29	80	3	3.3	3.3	3–6	225	59	62	14.3	23.8	20.6	43.4
Sodium sulfamethylthiazole	7			2	8.3	8.7	12–24	700	58	77	35.1	47.6	15.0	33.3
	9			6	5.8	6.3	2–6	490	61	71	29.0	53.0	8.6	31.6
	14	32	66	3†	5.3	6.0	3–6	520	58	62	33.0	40.5	30.7	58.3

5 per cent glucose in distilled water between 90 and 100° C.* Boiling was avoided after the sulfathiazole was added. The oral and rectal doses were dissolved or suspended in tap water, using 500 ml. for the former and 300 ml. for the latter. Each subject was given a soap and water enema a few hours before rectal administration of the drugs.

No untoward reactions, local or general, followed the subcutaneous or rectal doses of any of the drugs. Some nausea accompanied the oral administration in most instances and several of the subjects vomited at or shortly after the completion of the intravenous injections.

Blood samples (oxalated) were taken at frequent intervals during the first 12 hours and at 12- to 24-hour intervals thereafter. All urines were saved and, in almost all instances, urine was obtained at the same time as the blood. Collections were continued until the urine showed no measurable amounts of drug—usually 96 hours or longer. Since there was rarely any significant amount of drug excreted after 72 hours, however, the figures are plotted to that time. A further period of 24 hours or longer was allowed to elapse before commencing a second study on the same subject.

Determinations of free and conjugated drugs in body fluids were carried out by the method of Bratton and Marshall,[2] using the Klett-Summerson colorimeter with No. 540 filter. Bile was usually diluted 1 : 10 with distilled water, and a trichloracetic acid filtrate prepared from this dilution. In some instances turbidity, which persisted after centrifugation and filtration, made these determinations impossible. For the assay of organs, wet tissue (about 5 grams) was weighed, finely divided, then ground with sand and extracted three times with boiling distilled water. The determinations were then carried out on the watery extracts as for blood.

For the determinations on feces, the total output for 24 hours or more was mixed with warm acetone, dried to a constant weight and thoroughly pulverized. Duplicate 1 gram samples of the powdered feces were then placed in Soxhlet thimbles and extracted thoroughly with acetone. Usually about 250 ml. of acetone and 16 hours or more of extraction were required to complete this process. The acetone extracts were then diluted 1 : 10 with distilled water and the determinations were made on 0.5 to 1.0 ml. amounts of this dilution treated in the same manner as blood filtrates. This part of the study was carried out by Miss Margaret A. Adams.

Results

Blood Concentrations and Urinary Excretion after Intravenous, Subcutaneous and Oral Administration of a Single 5-gram Dose of Sulfonamide Compounds. The essential data are summarized in table 1 and in figures 1 to 4. Maximum blood levels were attained immediately after the intravenous injection and, with few exceptions, within two to three hours after the oral administration of all the drugs studied. Following subcutaneous

* Bactericidal tests indicated that this solution was highly active against the pneumococcus.

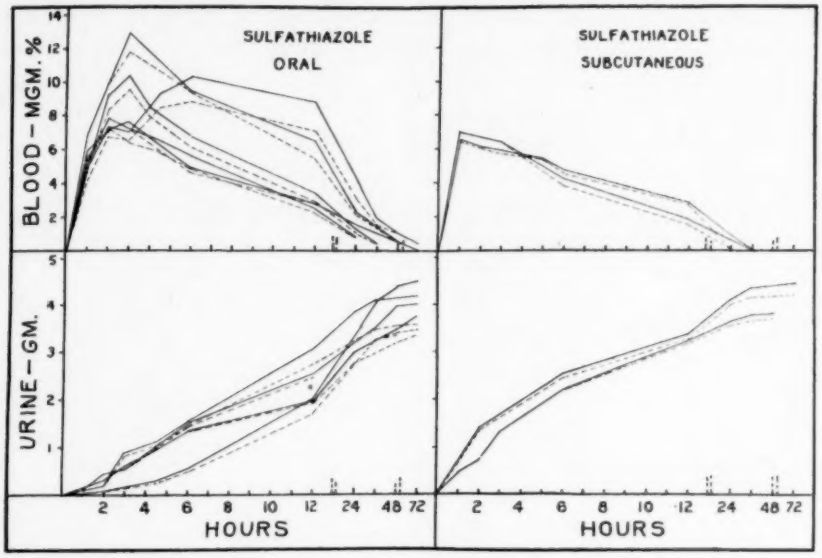

FIG. 1. Blood levels and cumulative urinary excretion of sulfathiazole after oral and subcutaneous administration of a single 5-gram dose in human subjects.

In figures 1 to 5 the solid line represents "total" drug and the dotted lines represent "free" drug. Each solid line and its corresponding dotted line are from one patient.

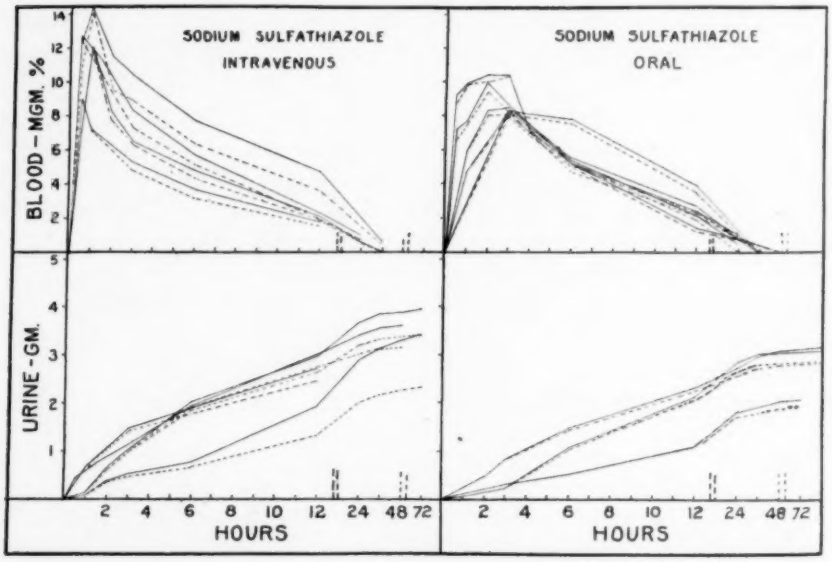

FIG. 2. Blood levels and cumulative urinary excretion of sodium sulfathiazole after intravenous and oral administration of a single 5-gram dose in human subjects.

administration, maximum levels of sulfathiazole in the blood were reached more promptly than in the case of sulfanilamide. With the latter, however,

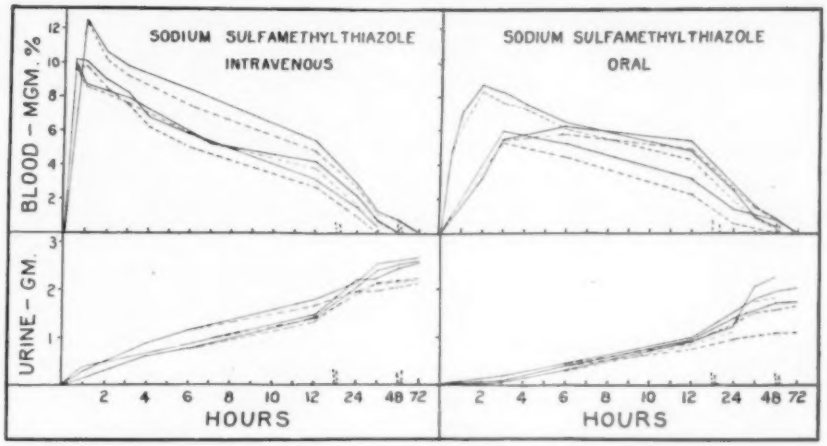

FIG. 3. Blood levels and cumulative urinary excretion of sodium sulfamethylthiazole after intravenous and oral administration of a single 5-gram dose in human subjects.

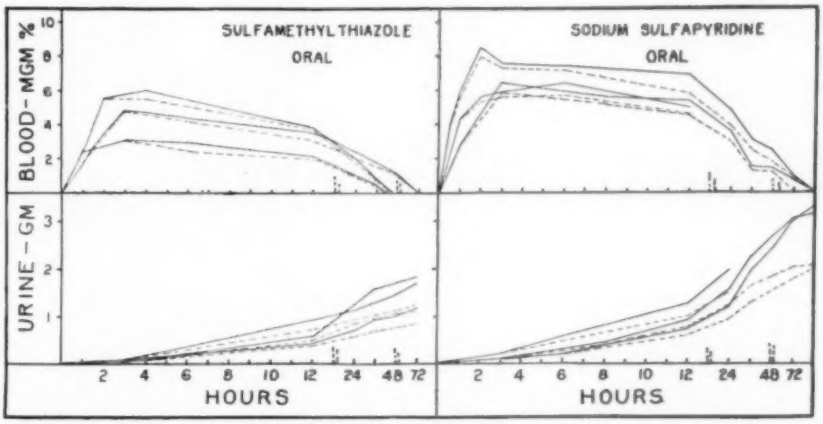

FIG. 4. Blood levels and cumulative urinary excretion after oral administration of a single 5-gram dose of sulfamethylthiazole and sodium sulfapyridine in human subjects.

the maximum blood levels were higher. Higher levels were obtained in the blood after intravenous and oral administration of the sodium salts than when the drugs themselves were given orally.* With similar doses, sodium sulfathiazole, given by mouth or by vein, yielded higher blood levels than any of the other compounds studied.

The relative amount of conjugated sulfathiazole and sulfamethylthiazole in the blood remained small regardless of the route of administration (figures 1 to 4). This is in sharp contrast to the percentage of acetylated sulfanilamide and sulfapyridine in the blood, which increases steadily with time.[1]

* In the case of sulfapyridine, no blood samples were obtained for 5 hours after its oral administration so that the data do not permit this comparison.

The time of maximum urinary excretion varied with the drug given, with the route by which it was administered and also in individual subjects, but it always occurred within the first 24 hours. In most instances the maximum urinary excretion occurred soon after the maximum blood level was reached. As with the blood levels, sulfathiazole and its sodium salt showed the highest concentrations in the urine regardless of the route of administration, and the maximum excretion occurred earlier than with the other drugs.

The most complete recoveries of administered drugs were obtained following their intravenous and subcutaneous injections. Within the limits of the methods, the results indicated that, after parenteral injection, the elimination of sulfanilamide, sulfapyridine and sulfathiazole in the urine was essentially quantitative. This was not true of sulfamethylthiazole of which only 60 per cent appeared in the urine. Following oral administration, the amount of drug recovered from the urine averaged slightly less than after the parenteral injections.

The proportion of the total urinary excretion which occurred during the first 24 hours offers further comparisons. With sulfathiazole, about 90 per cent of the urinary excretion of the drug usually occurred within 24 hours (range: 70 to 95 per cent), whereas with the other drugs this proportion was usually about 70 per cent (range: 45 to 85 per cent). The route of administration had only a minor effect in this respect. The relative amounts excreted in this period were the same for each drug and for its sodium salt, except after the oral administration of sodium sulfapyridine. A smaller part of the excretion of the latter salt occurred in 24 hours, as compared with the amount excreted during the same period when sulfapyridine was given orally.

Most striking are the differences in the degree of conjugation of the various drugs found in the urine, particularly during the first 24 hours after their administration. The smallest percentage of conjugation in the urine was found with sulfathiazole, and the largest with sulfapyridine. With the former, the proportion of the drug recovered in the urine in conjugated form during the first 24 hours was sometimes as low as 2.4 per cent; with the latter it was as high as 76 per cent. Sulfamethylthiazole showed slightly more conjugation than sulfathiazole, and sulfanilamide somewhat less than sulfapyridine. In the case of each drug the percentage of the excreted drug which was conjugated was essentially the same regardless of the route of administration. Sodium sulfapyridine given by mouth appears to be an exception in that less of the excreted drug was acetylated than was the case after its intravenous injection or after the oral administration of sulfapyridine.

That individual subjects may vary with respect to the extent to which they conjugate these drugs is most clearly illustrated by Subject 4. Following the intravenous injection of sodium sulfapyridine and after the oral ad-

ministration of sulfapyridine, this subject's urines contained the same total amount of drug but less than half as much conjugated sulfapyridine as was found in any of the other subjects who received the same materials in a corresponding manner.

Blood Levels and Urinary Excretion after Rectal Administration of a Single 5-Gram Dose (Table 2 and Figure 5). Sulfanilamide was absorbed fairly rapidly following its rectal administration. The maximum levels were reached in the blood 3 or 4 hours after its administration and were somewhat lower than when the oral route was used. From 41 to 68 per cent of the administered drug was excreted in the urine, and from 40 to 48 per

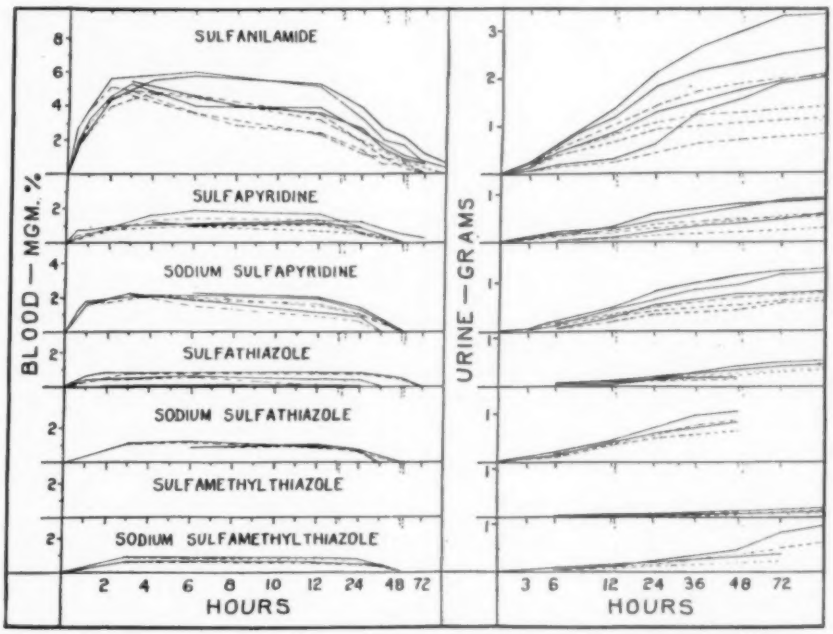

FIG. 5. Blood levels and cumulative urinary excretion after rectal administration of a single 5-gram dose of various sulfonamide compounds in human subjects.

cent of the drug recovered in the urine was acetylated. Most of the urinary excretion of the drug occurred in the first 48 hours, and less than 2 per cent of the total amount was recovered after 96 hours. Only 12 per cent of the administered drug was recovered from the feces of the 2 subjects in whom this was determined.

The other drugs were all poorly absorbed. The sodium salts were absorbed somewhat better than the corresponding drugs. Sulfapyridine was absorbed somewhat better than sulfathiazole so that the blood levels were higher and a larger percentage of the administered sulfapyridine was recovered from the urine.

TABLE II

Urinary Excretion and Maximum Blood Concentrations of Sulfonamide Compounds after Rectal Administration of a Single 5-Gram Dose

Compound	Subject	Maximum Blood Concentration			Mg. of Drug Excreted in Urine				Recovered from Feces				Per Cent of Administered Drug Recovered from	
					First 24 Hours		96 Hours		First Stool		Second Stool			
		Hours After Administration	Mg. Per Cent						Hours After Administration	Mg.‖	Hours After Administration	Mg.‖	Urine*	Feces*
			Free	Total	Free	Total	Free	Total						
Sulfanilamide	5	4	4.7	5.5	452	633	800	2038	35	578			41	12
	7	3	4.9	5.3	910	1305	1202	2045					41	
	7	3	4.6	5.4	1093	1813	1375	2633	3	575	24	10	53	12
	12	3	4.9	5.7	1440	2149	2017	3385					68	
Sulfapyridine	5	12	1.1	1.3	146	231	303	540					11	
	7	6	1.4	1.9	383	596	525	868					17	
	9	6	1.0	1.1	328	468	534	866	24	2831			17	57
Sodium sulfapyridine	7	4	2.1	2.1	531	849	789	1313					31	
	8	3	2.2	2.2	423	687	651	1269	48	1380			30	32
	8	6†	2.0	2.2	361	566	616	817	24	2322	72	2	19	54
Sulfathiazole	5	6	0.9	0.9	125	183	347	545					11	
	8	4	Tr.	Tr.	133	173	164	212	24	3621			4	72
	12	6	0.6	0.6	166	200	363	451	54	2300‡			9	46
Sodium sulfathiazole	8§	6	1.1	1.1	527	633	676	832	24	2678	48	28	19	63
	10§	12	1.0	1.0	585	720	852	1080	14	1634	48	48	25	38
Sulfamethylthiazole	8§	All	0	0	36	68	47	95	24	1902			2	38
	9	All	0	0	59	93	131	228						
Sodium sulfamethylthiazole	7	6	0.9	0.9	127	211	230	363	24	3357			8	78
	10	6	0.6	0.6	155	218	619	997	12	729	48	65	23	18

See also figure 5.

* The percentage of the sodium salts excreted is corrected both for sodium and for water of crystallization.

† First blood taken. ‡ Done by water extraction. § No drug found in urine or stool after 48 hours. ‖ Total drug.

In most instances where determinations were made on the feces, it was possible to recover a large proportion of the administered drug in the first stool passed. Regardless of the amount recovered from the first stool and the time when it was passed, however, only very small additional amounts were recovered from subsequent stools. Almost all of the drugs recovered from the feces were in the unconjugated form. The total amounts recovered from both urine and feces varied widely. In some instances as much as three-fourths of the administered drug was recovered from the feces 24 hours after it was given.

Blood Levels and Urinary Excretion after Administration of 5 Grams of the Acetyl Derivatives of 3 Sulfonamide Compounds. The results of the few studies made with acetyl compounds are shown in table 3. Only acetylsulfanilamide was absorbed to any considerable extent. Even with this drug, the maximum blood level attained was lower and the total amount of drug recovered from the urine was less than after the ingestion of sulfanilamide. The maximum blood levels after the oral administration of acetylsulfapyridine were only 2.1 and 2.4 mg. per 100 ml., and only from 20 to 32 per cent of the administered drug was recovered from the urine. The highest blood level in the subject who received acetylsulfathiazole orally was 0.7 mg. per 100 ml., and he excreted into his urine a total of 7 per cent of the ingested drug. The percentage of drug found in the blood and urine in the unconjugated form was always small. In the one subject who received the acetylsulfathiazole, the small amount recovered from his urine showed a considerably greater unconjugated portion than was found in any of the subjects who received acetylsulfanilamide or acetylsulfapyridine. One subject given acetylsulfapyridine directly into the duodenum (as verified by fluoroscopy) likewise showed very little absorption into the blood or excretion into the urine.

Distribution of Sulfonamide Compounds between Blood Plasma and Red Blood Cells. This was studied for the " free " drugs and the data are shown in table 4. Sulfanilamide was found in higher concentrations in the cells than in the plasma. For this drug, the ratio of the concentration of the drug in the cells to that found in the plasma was about 10 to 7. Sulfapyridine, however, occurred in slightly greater concentration in the plasma than in the red blood cells. If the concentrations are expressed in terms of the water content of the cells and of the plasma, however, they are practically equal.*

The distribution of sulfathiazole and sulfamethylthiazole, however, is different. The distribution ratio for sulfathiazole, except after its subcutaneous administration, varied from 1.4 to 2.6. In general, the ratio of

* Some of the data concerning sulfanilamide and sulfapyridine are taken from the previous study.[1] The actual water contents were not determined. However, if one assumes values of 0.64 and 0.91 per cent for the water content of cells and plasma, respectively, the ratio of the concentration in plasma water to that in cell water would be 0.7 times P/C (table 4). These values were also assumed in the calculation of renal clearances.

TABLE III

Blood Concentrations and Urinary Excretions after Administration of a Single 5-Gram Dose of the (Para-) Acetyl Derivative of 3 Sulfonamide Compounds

Compound and Route of Administration	Subject	Hours after Administration	Blood		Urinary Excretion					Per Cent of Administered Drug Excreted	Per Cent of Excreted Drug Unconjugated
			Mg. Per Cent		Volume (ml.)	Mg. Per Cent		Amount (mg.) Cumulative			
			Free	Total		Free	Total	Free	Total		
Acetylsulfanilamide (Oral)	9	1	0.4	3.4	80	4	48	3	38		
		3	0.6	6.4	120	14	132	20	204		
		6	0.6	5.4	140	22	220	51	512		
		12	0.6	4.2	380	19	86	122	838		
		24	0.3	2.3	1400	12	75	283	1885	44	15
		36	T	1.6	1900	8	38	429	2603		
		48	T	1.2	950	7	33	491	2918		
		72	0	0.1	2200	3	9	548	3109	72	18
Acetylsulfapyridine (Oral)	6	1	0.0	0.3	60	1.4	9.4	1	6		
		2	0.3	1.2	230	1.6	4.7	5	17		
		3	0.3	1.2	280	2.2	4.7	11	30		
		6	0.4	2.4	1000	3.1	24	42	271		
		12	0.7	2.2	1000	2.7	65	69	921		
		24	0.4	0.5	900	16	81	83	994	23	8
		36	0.4	0.4	1400	3.4	9.2	130	1123		
		48	0.6	0.9	600	2.7	7.1	146	1165		
		72	0.0	0.0	1700	1.6	9.3	174	1324		
		96	0.0	0.0	2400	0.6	1.3	188	1355	32	14

TABLE III—*Continued*

Compound and Route of Administration	Subject	Hours After Administration	Blood		Urinary Excretion					Per Cent of Administered Drug Excreted	Per Cent of Excreted Drug Unconjugated
			Mg. Per Cent		Volume (ml.)	Mg. Per Cent		Amount (mg.) Cumulative			
			Free	Total		Free	Total	Free	Total		
Acetylsulfapyridine (Oral)	12	1	0.0	0.8	300	0.0	1.6	0	5		
		2	0.6	1.8	200	1.0	16.3	2	38		
		3	0.6	2.1	300	1.6	18.4	7	93		
		6	0.8	1.5	300	5.2	66.3	23	292		
		12	0.6	0.7	800	2.8	21.4	45	463		
		24	0.6	0.5	675	3.6	17.1	69	578	14	12
		48	T	T	2700	1.2	4.5	101	700		
		72	0.0	0.0	2600	1.5	3.5	140	791		
		96	—	—	3100	0.7	1.9	162	850	20	18
Acetylsulfapyridine (Duodenal)	12	½	0	0.6	400	0	1.1	0	4		
		1	0	0.7	140	0.8	6.0	11	13		
		2	0	0.8	220	2.7	8.4	17	31		
		3	0	0.7	115	1.2	14.2	19	48		
		6	0	0.8	800	0.7	8.6	25	116		
		12	0	0.3	300	3.2	19.5	34	175		
		24	0	T	820	1.9	10.8	50	264	6	19
		36	0	0	2200	0.7	3.8	65	247		
		48	0	0	825	1.8	6.9	80	404		
		72	0	0	2600	1.2	4.3	111	516		
		96	0	0	2500	1.2	5.9	141	663	15	22
Acetylsulfathiazole (Oral)	7	1	0	T	210	1.4	2.8	3	6		
		3	T	T	440	1.4	5.8	9	31		
		6	T	0.7	300	6.3	23.0	28	102		
		12	0	T	1250	3.0	8.6	66	209		
		24	0	T	1700	2.0	3.5	100	269	6	37
		36	0	0	1900	0.7	1.1	113	290		
		48	0	0	1800	0.7	0.7	125	302	7	41

T = trace.

TABLE IV

Distribution of Sulfonamide Compounds (Unconjugated) between Blood Plasma and Red Blood Cells

Compound	Subject	Route of Administration	Time After Drug Given or Added	Concentration (mg./100 ml.)			$\frac{P}{C}$	Hematocrit (corrected)
				Whole Blood	Plasma (P)	Cells (C) (calculated)		
Sulfanilamide	13	*	10 minutes	8.5	7.6	9.4	0.8	50.2
			3 hours	9.7	7.4	12.0	0.6	50.2
	15	*	10 minutes	9.7	7.7	11.9	0.6	46.9
			3 hours	9.3	7.5	11.3	0.7	46.9
Sulfapyridine	16	Oral	†	4.6	4.7	4.4	1.1	33.0
	17	Oral	†	9.5	10.4	8.2	1.3	39.0
	18	Oral	†	19.0	19.2	18.7	1.0	40.0
Sodium sulfapyridine	7	Venous	30 minutes	6.8	7.5	5.7	1.3	42.0
	13	*	10 minutes	8.1	8.7	7.6	1.1	50.2
			1 hour	8.1	8.8	7.4	1.2	50.2
	15	*	10 minutes	8.3	8.7	8.0	1.1	46.9
			3 hours	8.2	8.6	7.7	1.1	46.9
	16	*	10 minutes	7.7	8.2	7.0	1.2	41.8
Sulfathiazole	7	Subcutaneous	3 hours	6.2	9.2	1.9	4.8	40.9
			5 hours	5.4	7.8	2.1	3.7	41.8
	8	Subcutaneous	2 hours	7.3	11.2	2.8	4.0	45.8
	17	Oral	†	2.3	2.7	1.5	1.8	45.2
Sodium sulfathiazole	11	Oral	3 hours	8.1	11.0	4.2	2.6	43.4
	7	Venous	30 minutes	12.6	16.3	7.7	2.1	43.0
	18	Venous	1 minute	26.0	28.5	17.3	1.6	22.0
			30 minutes	13.7	15.1	8.6	1.8	22.0
	6	Venous	1 hour	12.0	13.8	9.5	1.5	43.0
			3 hours	6.3	7.6	4.7	1.6	43.0
	5	Venous	50 minutes	14.5	16.1	11.4	1.4	33.4
Sulfamethylthiazole	7	Oral	1 hour	1.9	2.9	0.5	5.8	43.1
			3 hours	4.0	6.0	1.0	6.0	40.1
	19	Oral	2 hours	2.0	3.4	0.4	8.5	46.0
Sodium sulfamethylthiazole	9	Venous	1 hour	12.4	20.4	1.9	10.7	43.0
			3 hours	9.2	15.2	1.5	10.1	44.7
	20	Venous	2½ hours	13.2	19.2	5.5	3.5	43.9

* Added in vitro.
† Patient under treatment.

the concentration of sulfathiazole in the plasma to that in the red blood cells was about 1.8 to 1, or about 1.3 to 1 on the basis of water content. After

subcutaneous administration of this drug the ratio was higher. The possible significance of this finding will be discussed later.

Sulfamethylthiazole penetrated the red blood cells even less than sulfathiazole. The concentration of this drug in the cells was only one-third to one-tenth of that found in the plasma.

Renal Clearances of Sulfathiazole and Sulfamethylthiazole and Their Distribution in the Body. The clearances for sulfanilamide and sulfapyridine as previously given[1] indicated considerable degrees of tubular reabsorption which varied a great deal in individual subjects. The data for sulfathiazole (table 5) indicate that, in general, there was less tubular reabsorption of this drug than of either sulfanilamide or sulfapyridine. Furthermore, the rate at which the blood was cleared of sulfathiazole was more uniform in different subjects than was the case with the other two drugs. On the other hand, sulfamethylthiazole or its sodium salt was cleared from the blood at a much lower rate, indicating a considerably greater degree of tubular reabsorption. The estimations were made on "total" (free and conjugated) drug,* since the amount of conjugated drug in the blood was always small.

It was also estimated from the available data that sulfathiazole was apparently distributed in a portion of the body considerably in excess of the extracellular water but less than the total body water. Sulfamethylthiazole gave variable results in different subjects. In two individuals (Numbers 9 and 20) the data suggested that the drug was confined essentially to the extracellular water, while in a third subject (Number 8) data obtained on two separate occasions suggested that the drug was distributed throughout most of the body water. Possible explanations of the latter differences will be discussed later.

Concentration of Drugs in Body Fluids and Organs of Patients Who Died while Under Treatment (*Table 6*). Most of the studies were done on patients who died within a few hours of the time the last dose of drug was given. In five of the sulfapyridine treated cases, no drug had been given for 16 hours or more before the time of death. The concentration of the drugs in the blood obtained from the heart varied considerably, as did the percentages of the drugs that were conjugated. In general, the patients who had high blood non-protein nitrogen levels before death also had, at autopsy, high concentrations of drug in the blood with large proportions of it in conjugated form. The sulfathiazole treated cases had the lowest percentage of conjugation in the blood. Since there were considerable variations among the findings in different patients, only the general trends of the findings in the fluids and organs in relation to the blood concentrations will be mentioned.

In the spinal fluids, the levels were generally lower than in the blood. Sulfathiazole showed the greatest and most constant difference in this respect, the spinal fluid levels all being about one-third of those found in the

* Distributions of "total" drug between serum and cells were used for this purpose.

TABLE V

Renal Clearances of Sulfathiazole and Sulfamethylthiazole after Administration by Various Routes

Compound	Route	Subject	Length of Period (minutes)	Average Serum Concentration for Period (mg./100 ml.)*	Total Drug Excreted in the Period (mg.)*	Blood Cleared (ml. per minute)	*Apparent* Distribution (per cent of body weight)
Sulfathiazole	Oral	6	180	7.0	667	53	
		6†	180	7.2	819	63	
			360	4.3	596	38	
		7	120	8.5	684	67	
			360	5.7	995	49	
		5	360	9.5	1437	40	
	Subcutaneous	7	240	7.5	1137	63	
			360	5.1	832	45	
		8	180	7.8	874	62	
			360	4.5	1013	63	
Sodium sulfathiazole	Oral	7	180	7.2	668	52	
			360	4.3	834	54	
		9	360	5.3	607	32	
		11	180	10.7	833	45	
			360	7.4	1054	40	
	Intravenous	5	360	6.1	1133	51	42
		6	180	6.4	958	83	38
			360	4.0	962	67	
		7	180	8.3	757	51	38
			360	4.7	1084	64	
Sulfamethylthiazole	Oral	9	540	6.6	816	25	
			720	4.8	230	7	
		13	180	5.2	144	15	
			360	4.2	216	14	
Sodium sulfamethylthiazole	Oral	7	180	10.8	231	12	
			360	8.4	533	18	
		9	360	8.9	554	17	
		14	180	8.8	322	20	
			360	6.3	506	22	
	Intravenous	8	120	8.3	295	29	69
			360	5.8	632	30	
		8†	300	6.4	435	23	55
			720	4.3	627	20	
		9	180	14.6	297	11	22
			360	12.8	678	15	
		20‡	140	19.3	582	25	31

* Sulfathiazole or sulfamethylthiazole.
† Separate experiment on same subject.
‡ Age 14 years, weight 45 Kg.

TABLE VI

Concentration of Sulfanilamide, Sulfapyridine and Sulfathiazole in

TABLE VI

Concentration of Sulfanilamide, Sulfapyridine and Sulfathiazole in Body Fluids and Organs of Patients Dying While Under Treatment with These Drugs

Case	Sex	Age	Diagnosis	Days of Drug Therapy	Total Dose (gm.)	Hours from Last Dose to Death	Hours from Death to Autopsy	Antemortem Blood Non-Protein Nitrogen* (mg. %)	Concentration in Body Fluids (mg. per 100 ml.)								Concentration in Organs (mg. per 100 gm. of tissue)									
									Heart's Blood		Cerebro-Spinal Fluid		Bile		Bladder Urine		Kidney		Liver		Lung‖		Spleen		Brain	
									F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T
Sulfanilamide Treated Cases																										
1	M	33	Erysipelas; alcoholism	4	12	3	9	29	4.3	8.1	3.3	4.4	16.0	26.0	63.6	206.6	4.2	7.5	5.0	6.9	3.0	5.0	3.1	5.1	3.6	5.0
2	M	70	Erysipelas; septicemia	4	22	8	18	29	10.1	17.5	7.9	9.5	—	—	38.9	100.1	15.5	16.5	14.7	18.1	10.5	12.8	8.2	9.8	—	—
3	M	39	*Staph. aureus* meningitis	2	8	4	14	40	4.7	7.0	—	—	—	—	11.2	23.2	4.0	5.2	3.8	4.7	5.3	7.6	3.4	5.1	2.2	2.3
4	M	1	Influenzal meningitis	3	14	7	6	26	—	—	—	—	—	—	—	—	18.8	23.2	20.7	21.7	19.8	20.7	19.2	21.5	18.3	18.3
Sulfapyridine Treated Cases																										
5	F	52	Pneumococcal meningitis	6	33	33†	19	39–119	15.3	41.2	6.4	14.7	8.0	17.7	53.6	225.1	36.5	58.0‡	18.5	20.6	10.8	26.4	6.2	14.1	2.2	3.3
6	F	9/12	Influenzal meningitis	5	8	8	16	—	4.1	5.7	3.6	4.7	6.4	8.9	—	—	8.5	10.5	—	—	4.7	6.3	7.2	7.5	3.5	3.5
7	M	3/12	*Staph. aureus* sepsis	3	5	6	19	—	21.5	23.7	16.2	16.7	30.2	31.8	—	—	22.3	22.3	18.5	18.5	18.5	18.5	21.8	21.8	16.3	17.1
8	M	60	*Strep. fecalis* endocarditis	4	12	9	12	89	7.2	9.5	—	—	—	—	48.3	82.9	14.5	19.1	5.0	5.8	5.3	6.6	—	—	—	—
9	M	71	Pneumonia; endocarditis	7	41	18	3	59–80	4.4§	17.8§	1.9	5.3	—	—	32.0	200.0	9.3	28.9	3.9	8.4	3.4	12.0	3.5	10.6	1.6	1.9
10	F	41	Pneumococcal meningitis	6	33	16	96	25–41	11.8	13.3	10.0	10.0	—	—	—	—	31.0	36.0	15.0	16.0	—	—	15.0	16.0	—	—
11	M	70	Pneumococcal meningitis	1	8	6	13	31	13.9	15.3	11.8	12.5	—	—	—	—	47.0	49.0	21.0	22.0	—	—	—	—	—	—
12	M	51	Pneumococcal meningitis	5	31	35	7	27–115	23.4	28.4	13.8	16.0	—	—	89.4	109.0	43.6	50.8	26.4	30.4	—	—	—	—	—	—
13	F	53	Lobar pneumonia	5	30	5	10	31	11.3	13.3	—	—	10.6	14.5	104.0	154.0	23.2	26.0	14.9	15.8	—	—	—	—	—	—
14	M	80	Lobar pneumonia	7	22	96	2	60–140–75	Trace	1.8	—	—	—	—	24.8	49.8	2.6	4.9	Trace	1.9	—	—	—	—	—	—
15	M	41	Pneumonia; meningitis	18	69	3	22	32	6.0	10.5	4.3	5.7	—	—	151.0	254.0	20.4	30.6	7.5	8.9	—	—	—	—	4.8	5.7
Sulfathiazole Treated Cases																										
16	M	65	Lobar pneumonia	2	9	7	7	43	5.0§	7.3§	1.5	1.9	9.3	9.8	55.5	76.7	17.1	20.2	7.3	7.7	4.6	5.8	5.1	6.7	—	—
17	F	63	Lobar pneumonia	12	52	6	4	53	3.3	4.0	1.2	1.4	—	—	219.6	254.4	11.3	15.5	2.5	2.5	3.6	4.4	3.5	3.6	2.2	2.2
18	M	48	Lobar pneumonia	7	40	12	3	55–67–34	1.7	2.1	—	—	3.4	5.8	118.1	178.6	3.9	5.1	3.1	3.9	1.5	1.6	2.3	2.7	—	—
19	M	68	Miliary tuberculosis	18	76	12	7	44–75–56	11.8	16.5	3.5	6.0	—	—	27.7	70.0	19.0	27.0	13.0	14.7	10.7	14.3	10.9	13.1	—	—

F = free. T = total.

* The first and last determinations are given. When the levels rose and subsequently declined, the highest level is also given.

Case 2. Gastric content 117.6 mg. per cent free and total.

Case 5. Ascitic fluid 24.0 and 61.1 mg. per cent free and total, respectively.

Case 13. Pericardial fluid 12.1 and 15.4 mg. per cent free and total, respectively.

† Drug stopped because of hematuria and oliguria.

‡ Medullary portion 36.1 and 71.7 mg. per cent free and total, respectively. Bloody material in kidney pelvis 153 and 388 mg. per cent free and total, respectively.

§ Clotted—determination made on serum.

‖ Consolidated portion used in pneumonia cases.

blood. Sulfanilamide and sulfapyridine showed wide variations, the spinal fluid levels ranging from one-third to four-fifths of blood levels. The proportion of drug in the conjugated form was essentially the same in spinal fluid and blood with sulfapyridine and sulfathiazole, but was lower in the spinal fluid with sulfanilamide.

The bile contained the drugs in higher concentration than the blood, but the proportion of the free and conjugated forms was essentially the same. In Case 5 there was less sulfapyridine in the bile than in the blood, but there were other similar discrepancies in this case.

The bladder urine contained high concentrations of drug in each instance, the levels ranging from 3 to more than 50 times the concentrations in the blood. In most cases, from one-half to four-fifths of the sulfanilamide and sulfapyridine in the urine was conjugated, whereas two-thirds or more of the sulfathiazole in the urine was in the " free " form.

With respect to the concentration of the drugs in the kidney, there was a striking difference between sulfanilamide, on the one hand, and sulfapyridine and sulfathiazole, on the other. Sulfanilamide was found in the kidney in concentrations which were essentially the same as in the blood and not very different from those found in the other organs. Sulfapyridine and sulfathiazole were usually present in the kidney in two or more times the concentration found in the blood or in any of the other organs (Case 7 is the only exception). When samples of medulla and cortex were studied separately, the former sometimes showed a slightly higher concentration than the latter, particularly of the acetylated drug (cf. Case 5).

In the liver, more than half of the cases showed more " free " drug than was found in the blood or in the other organs (except the kidney). However, the amount and percentage of conjugated drug in the liver were lower in almost every instance. The latter difference was most striking when the blood contained a high concentration of conjugated drug. The findings in the liver were similar for each of the three drugs.

In the lung and spleen, the concentrations of the drugs were essentially the same or slightly lower than in the blood. In the brain, however, the drugs were usually present in much lower concentrations than in the other organs.

Discussion

The results of the studies on the absorption and excretion of sulfanilamide and sulfapyridine are essentially in accord with those of other workers.[3, 4, 5] The only new feature brought out here concerns the oral administration of sodium sulfapyridine. In the three subjects presented here and in a limited number of observations made on patients, the degree of acetylation, both in the blood and in the urine, was regularly less when the sodium salt was given by mouth than when sulfapyridine itself was used in the same manner. No other differences were noted. In view of the prob-

able importance of the acetylsulfapyridine in the causation of renal complications,[6, 7, 8] this may be of some clinical significance.

Many of the findings concerning the absorption and excretion of sulfathiazole have already been noted by other workers, both in animals [9, 10] and in man.[11, 12] Sulfathiazole was found to differ from both sulfanilamide and sulfapyridine in three important respects: (1) It was absorbed more rapidly after its oral administration and gave higher levels earlier. (2) It was excreted more rapidly into the urine, the maximum excretion occurring earlier and a larger proportion of the ingested drug being recovered during the first 24 hours. (3) A smaller percentage of the drug found both in the blood and in the urine was in the conjugated form. The latter is probably dependent, in part at least, on the rapidity with which the drug is eliminated. That portion of the drug which is excreted after the first 24 hours is conjugated to a considerable degree.

Our observations indicated that sulfamethylthiazole and its sodium salt were not absorbed as well as the other drugs, and a smaller proportion of the administered drug was recovered from the urine. This was true regardless of the route of administration. The methyl compound was acetylated to a considerably greater extent than sulfathiazole. This is significant because the methyl compound and its acetyl derivative are both much less soluble than sulfathiazole and its acetylated form.

The studies concerning the rectal administration of the various drugs are of interest in view of some apparently conflicting reports.[11, 13, 14, 15] Our findings suggest that, of the compounds studied, only sulfanilamide is absorbed to any extent sufficient to warrant its use by this route clinically. The only other drug which was absorbed to any appreciable extent was sodium sulfapyridine, but even with this compound the low levels attained in the blood, the small percentage of administered drug recovered from the urine and the large amount found in the feces after 24 hours or longer indicate that it should not be recommended for use by the rectal route. The reported successes with its use may be related possibly to differences in absorption between infants and adults or to the use of larger doses or different methods of administering them.

The acetyl derivatives were all poorly absorbed. Observations in this laboratory and those of other workers have indicated that these derivatives are essentially devoid of antibacterial activity. From the results shown in table 3, it appears that these compounds are not deacetylated in the body to any appreciable degree after their oral or duodenal administration. Furthermore, in the few observations made, nausea and vomiting were certainly not less than with the parent compounds. These findings are of particular interest in view of the Danish report of the successful clinical use of acetylsulfapyridine in the treatment of pneumonia.[16]

In the previous study [1] it was shown that when glucose-sulfapyridine was added to human blood in vitro or administered parenterally, the sulfapyridine

was found almost entirely in the plasma. This was in sharp contrast to sulfanilamide, which was found in somewhat greater concentration in the red blood cells than in the plasma, and sulfapyridine, which was about equally distributed. From the present findings, it appears that the four drugs studied all varied with respect to their distribution between plasma and red blood cells. The drugs arranged themselves in this respect in the following order: (1) sulfanilamide, which, as already noted and as shown by others,[17, 18] occurred in greater concentration in the cells than in the plasma; (2) sulfapyridine, which occurred in somewhat greater concentration in the plasma but was about equally distributed between plasma and red cells on the basis of their water content (cf. also [18]); (3) sulfathiazole, of which the concentration in the plasma was definitely greater than that in the cells; and (4) sulfamethylthiazole, which penetrated the red blood cells even less than sulfathiazole. The findings were essentially the same with the various compounds, with their sodium salts and with the different routes of administration, except in the case of sulfathiazole. When this drug was given subcutaneously it appeared to penetrate the red blood cells less than after its administration by other routes. This may be due to the fact that, in order to affect the solution of sulfathiazole in the desired concentration, it was added to hot 5 per cent glucose solution. The possibility that part of the drug was combined with the glucose during this process cannot be excluded, even though the resulting solution apparently retained its bactericidal activity. The resulting glucose-sulfathiazole may then have failed to penetrate the red blood cells, as was the case with the corresponding sulfapyridine solution.

The rate of renal clearance of sulfathiazole was somewhat higher than that of sulfanilamide and sulfapyridine, but it still indicated a fair amount of tubular reabsorption. On the other hand, sulfamethylthiazole and its sodium salt were cleared from the blood at a very low rate, which probably indicated considerable reabsorption from the glomerular filtrate.

The apparent distribution of sulfathiazole in the body fluids was in a volume of water somewhat greater than the extracellular fluid, but considerably less than the total body water. This finding is consistent with the poor penetration of this compound into the red blood cells and with the low concentrations of the drug found in the cerebrospinal fluid.

The data concerning the apparent distribution of sulfamethylthiazole are somewhat confusing. In two subjects the values suggested that the drug was essentially confined to the extracellular water, which is consistent with the findings already noted concerning the lack of penetration of this compound into the red blood cells. In the third subject, however, the data indicated a distribution throughout almost the total body water. There are some reasons to suspect that calculations based on the data concerning distribution of sulfamethylthiazole may not be satisfactory. The fact that only 60 per cent of the administered drug was recovered from the urine raises the question of whether a true estimate of the amount of drug available for

distribution can be made except in the very early period after its administration. Also, the drug, because of its insolubility, may be deposited, in part, in the bowel, and the concentration in plasma water would then not be representative of the concentration throughout the body water. Finally, the presence of large amounts of sulfamethylthiazole in the urine during certain periods may lead to crystallization of this drug at some stage of its determination. The evidence from the distribution between red blood cells and plasma is probably a more reliable index of what happens to this drug in the body than the calculation based on urinary excretion and serum water calculations.

Animal experiments have indicated that sulfanilamide is evenly distributed in the various tissues,[19] while sulfapyridine is distributed somewhat unevenly.[20] In dogs sacrificed 4 hours after the administration of sulfapyridine, Marshall and Litchfield [21] found the concentration of the drug to be higher in the liver than in the blood and other organs, but the kidney was not analyzed. In patients who died while under treatment with sulfapyridine, Brown et al.[5] found the concentration of drug high in the kidney, but their data showed a higher level in the lung in one case.

In our cases, death occurred three or more hours after the last dose of drug was given. Large amounts of the drugs were retained in the tissues for many hours. In two cases, very high levels were found after 33 and 35 hours, and in one case measurable amounts were detected although death occurred 96 hours after the last dose of drug had been given. A variable interval elapsed between death and the time the tissues were obtained for analysis, but the effect of this factor cannot be evaluated.

The concentration of sulfapyridine and of sulfathiazole was consistently found to be two or more times as high in the kidneys as in the other tissues. Sulfanilamide behaved differently in this respect, its concentration in the kidney being the same as in the other tissues. While nitrogen retention was associated with retention of the drugs in all tissues, this factor did not account for the specific retention of sulfapyridine and sulfathiazole in the kidneys. The concentration in this organ was significantly higher than in the other organs, regardless of whether or not there was retention of nitrogen or drug. Contamination with urine likewise fails to explain the higher levels in the kidney, since this factor was equally operative in the case of sulfanilamide.

Bettman and Spier [22] found higher levels in the bile than in the blood in patients with normally functioning gall-bladders. Our results indicate that this is also true for sulfapyridine and sulfathiazole. Under appropriate conditions it seems likely that these three drugs can be concentrated in the gall-bladder.

With all three drugs, the conjugated form was found in lower concentration in the liver than in the blood or in the other organs studied. This was more evident when the proportion of conjugated drug in the blood was

high. The concentrations of the unconjugated drugs, however, were frequently higher even when less conjugated drug was found. These findings are not entirely consistent with the concept that the liver is the site of acetylation of the sulfonamide drugs in humans, as was shown to be the case for sulfanilamide in rabbits.[23] However, we are not aware of any direct proof that the liver is the site of acetylation in humans.

The levels of sulfathiazole and sulfapyridine and, to a lesser extent, of sulfanilamide tended to be lower in the brain than in the blood. In the spinal fluid, however, the levels of sulfathiazole were consistently about one-third of those in the blood, while the concentrations of sulfapyridine and sulfanilamide, though variable, were frequently two-thirds or three-fourths of the blood levels. Our clinical experience also indicated that there was very little penetration of this drug into the spinal fluid even with moderately high blood levels, and Carey[24] has recently reported similar findings. From the point of view of therapy, these findings would suggest that sulfathiazole is not so desirable as the other drugs in the treatment of central nervous system infections.

Summary

Data are presented concerning the blood concentrations and urinary excretion of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole and of the sodium salts of the latter three drugs after the administration to human subjects of a single 5-gram dose by various routes.

In general, the sodium salts given intravenously or orally yielded higher blood levels and these levels were attained more rapidly than when the corresponding drugs were given by mouth. The highest levels were obtained with sodium sulfathiazole.

Sulfathiazole and its sodium salt were excreted more rapidly into the urine than either sulfanilamide or sulfapyridine. All the drugs, with the exception of sulfamethylthiazole, were excreted more or less quantitatively after intravenous or subcutaneous injection, and almost all of the administered drugs were recovered from the urine after their oral administration. Only about 60 per cent of administered sulfamethylthiazole was recovered from the urine, regardless of the route by which it was given.

Sulfathiazole showed the least amount of conjugation and sulfapyridine showed the most. After oral administration of sodium sulfapyridine, the percentage of acetylated drug in the blood and urine was considerably lower than that found after sulfapyridine itself was given by mouth.

Different subjects varied with respect to their absorption, excretion and conjugation of the different drugs. There were apparently fewer variations with sulfathiazole than with any of the other compounds.

Sulfanilamide was fairly well absorbed from the rectum. All the other drugs were poorly absorbed after rectal administration and this absorption was only slightly better when the sodium salts were used.

The para-acetyl derivatives of sulfanilamide, sulfapyridine and sulfathiazole were poorly absorbed after oral administration. The acetylsulfanilamide was absorbed somewhat better than the others. Only a small percentage of these drugs was deacetylated in the human body.

The four compounds were found to distribute themselves differently between the blood plasma and the red blood cells. Sulfanilamide was found in the red blood cells in greater concentrations than in the plasma, sulfapyridine was about equally distributed, sulfathiazole was present in somewhat greater concentrations in the plasma and sulfamethylthiazole was found mostly in the plasma.

Sulfathiazole was cleared from the blood at a rate which was greater, and sulfamethylthiazole at a rate which was lower than either sulfanilamide or sulfapyridine. The clearance rates of these drugs indicated varying degrees of tubular reabsorption which was greatest for sulfamethylthiazole and least for sulfathiazole.

Data are also presented concerning the concentration of sulfanilamide, sulfapyridine and sulfathiazole in body fluids and organs of 19 patients who died during treatment with these drugs. There were considerable variations among the different cases.

The concentrations of the drugs were higher in the bile and lower in the spinal fluids than in the blood. Sulfathiazole was present regularly in the spinal fluid in about one-third the concentration found in the blood.

Sulfapyridine and sulfathiazole were found in the kidney in considerably higher concentrations than in the blood and other organs. The concentrations of sulfanilamide were about the same in the various organs studied, including the kidney.

In the liver, the amounts of acetylated drug were always less, although the concentrations of free drug were frequently higher than in the blood. This was true of all three drugs.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1939

(Seventh Rheumatism Review) *

Part I

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General Incidence of Rheumatic Diseases: Social and Economic Importance

That the rheumatic diseases are a great universal menace was again shown by Tegner; his excellent survey of the problem as it affects the United States, England and Europe should be valuable to all students of "rheumatism." In Great Britain respiratory diseases were the first, nervous diseases next and rheumatic complaints were the third commonest cause for disability benefits.[482] The incidence of chronic rheumatic diseases in England, Wales and Scotland is "shocking," according to Davidson who with the aid of medical practitioners surveyed 100,000 persons in Scotland. Scottish physicians were required to spend 10 per cent of their time on rheumatic diseases, more than 300,000 persons (6 per cent of the total population of 5,000,000) in Scotland require care for these diseases yearly and more than 50,000 insured persons are totally incapacitated for an average of 60 days yearly. Among the insured population of Scotland about one of every 50 men and one of every 60 women were disabled by muscular rheumatism for a month.[482] Chronic arthritis is one of the commonest disabilities requiring monetary benefits to United States World War veterans.[801] In previous Reviews [5, 6] we have cited the incidence of rheumatic diseases in the United States as determined by the National Health Survey. Further data on the scope and method of that survey were given.[595]

The influence of climate on the incidence of rheumatic diseases was debated.

Tegner noted that local patriotism, rather than scientific data, often settled the question. Rheumatism was as common in the hills of Sweden as on the flat lands of Denmark and Holland; it is said to be more common in the cold, damp, seaside parts of England, yet in Scandinavia rheumatism sanatoria are generally placed by the sea. Physicians in European countries with much coast line favored the sea air for rheumatic patients; those in countries with little coast line regarded sea air as dangerous, but those in mountainous countries favored the altitude! Tegner concluded that in the temperate zone, local climate is an unimportant factor in the incidence of chronic rheumatism.

Of greater importance than the general climate is the "micro climate" of home and working place, according to Hill. Cold, damp, atmospheric electricity and cyclonic disturbances are not important. Eskimos and Lapps have much less rheumatism than dwellers in temperate zones who live indoors in badly ventilated, artificially heated city houses. Despite the cold, none of Scott's or Shackleton's arctic explorers had rheumatism; there is little rheumatism in the tropics where people live outdoors. Because of the heat and humidity of their surroundings women who make cotton goods are prone to suffer from atrophic arthritis.[596]

[The exact rôle which climate plays cannot be determined until studies are made under controllable experimental conditions.—Ed.]

Definition of "Rheumatism"

"What's in a name?" According to some,[380] "rheumatism" is a totally unscientific term which is used to include a wide variety of unrelated conditions. According to others "all forms of acute, secondary chronic, and

primary chronic rheumatism belong to one nosological entity, the protean appearance of which is not greater than that of tuberculosis" (Levinthal).

Classification of Diseases of Joints and Related Structures

The classification of the rheumatic diseases used in the Massachusetts General Hospital, Boston, was given again [5]; Bauer [51] carefully defined each term. The classification adopted at the Fifth Russian All-Union Conference on Rheumatism was also given (Artemiev).

Relative Frequency of the Rheumatic Diseases

The relative incidence of the various rheumatic diseases in the British Red Cross Society Clinic for Rheumatism [97] in London is given in table 1.

Table 1

Cases of British Red Cross Society Clinic

	Per cent		
	Men	Women	Total
Group A. With articular rheumatism			
1. Rheumatoid (atrophic) type			
a. Infective	9.7	11.1	10.6
b. Noninfective	2.4	5.7	4.5
2. Osteo-arthritic (hypertrophic) type			
a. Senile	13.0	14.7	14.1
b. Climacteric or other metabolic	3.6	10.7	8.1
3. Gout	8.2	2.1	4.4
4. Trauma	1.2	1.8	1.6
5. Miscellaneous (neuropathic, hemophilic and so forth)	4.0	2.4	3.0
Group B. With nonarticular rheumatism	52.7	46.8	46.7
Group C. Suffering from sequel of rheumatic fever	1.0	1.0	1.0
Group D. Suffering from nonrheumatic conditions	4.2	3.7	3.7

[The column of totals in table 1 does not add up to exactly 100 per cent. The last group (D) was probably sent in with supposed "rheumatism." To get the relative incidence of the "rheumatic cases" Group D should really be subtracted from the total group and the figures recalculated.—Ed.]

Diseases of Joints Related Primarily to Trauma

Traumatic Arthritis and Synovitis. Among 193 cases of athletic injuries to knees were 19 of synovitis, 59 of sprains to lateral ligaments, and 115 cases of injuries to semilunar cartilages.[394] Acute traumatic arthritis

and synovitis should generally be treated conservatively by rest, heat, light massage and early motion. Rest can be enforced by using bilateral rubber sponge splints surrounded by an elastic bandage [777] or by plaster casts with a removable top to permit massage and motion.[318] According to Funsten early aspiration of blood from an injured joint may be dangerous; it may prolong hemorrhage; the knee may not have reacted yet to the trauma and developed resistance to infection: such joints should not be aspirated until 48 hours after trauma, nor be operated on until four to seven days after trauma. Occupational therapy may hasten recovery.[416]

Excision of the patella was done by Berkheiser in two cases of traumatic arthritis in knees. The treatment of injuries of the acromioclavicular and sternoclavicular joints was described.[407] A method for gauging the amount of articular disability after injuries was reported.[733]

Sprains. Sprains should be treated by only a few days of rest, followed by use of the joint.[96] Local injections of novocaine, strapping of the joint with elastoplast, and then careful use of the part were recommended.[289]

Internal Derangements of Knees. Several articles thereon appeared.[96, 249, 297, 561, 569, 690, 731, 777] Diagnostic features of various derangements were reviewed.[489] Injections of air were considered of value in the diagnosis of internal derangements.[361] The commonest result of injury to knees is damage to the internal semilunar cartilage.[394, 659] Such injuries may not produce definite locking; according to Edmunds the most valuable symptom is instability of the knee. The results of Hopkins and Huston from surgical treatment (good in 65 per cent) were better than those from conservative measures (good in 45 per cent), but since conservative measures gave relief so often, surgical treatment was reserved for those not helped otherwise. Conservative measures were favored by others also: for semilunar injuries, reduction by manipulation in abduction, a plaster cast for three to four weeks, then the use of exercise and a Thomas heel,[249] or reduction of dislocation, aspiration, and use of bivalved cast [569]; for injuries to cruciate ligaments, immobilization for two to four months in a position of slight flexion.[249, 561]

Described were operations for the repair of the various ligaments of the knee.[137, 138, 506, 731, 780, 809] Good results were obtained in 83 per cent of Campbell's cases,[137] in 94 per cent of Schoenfeld's cases.

An experimental study of injuries to ligaments of knee joints in rabbits and in human cadavers was made by Horwitz [398]: in rabbits tears in the internal lateral ligaments healed regardless of the size of the defect and whether or not fixation was employed. Tears in cruciate ligaments did not heal during simple fixation, and the severed ends could be approximated surgically only early after injury. Satisfactory results of conservative fixation in humans with tears in cruciate ligaments are really due to healing of associated injuries to the collateral ligament.

Bone Rarefaction after Articular Trauma. After trauma to a wrist or ankle, bones of adjacent hand or foot may rarefy, and regressive changes may occur in overlying tissues (muscular atrophy, vasomotor and trophic

changes in skin, perhaps swelling of soft parts). The pathology of Sudeck's atrophy or Leriche's disease is unknown. According to Jaffe long bones may likewise rarefy after trauma (without fracture) to large joints. Biopsies in two such cases indicated that rarefaction was due to hypervascularization of affected tissues especially of cortical bone, and pain arose from functional strain on weakened bones. Recovery is favored by physical therapy and *use* of affected parts.

Penetrating Wounds. Perforating and penetrating wounds of joints, such as result from air-attacks in war, demand early excision of the wound.[288, 319, 540, 541, 601, 743] Recommended were articular lavage with normal saline or a mild antiseptic solution, removal of foreign bodies, suturing the synovial membrane, and packing the cutaneous wound with vaseline gauze. Immobilization of the part in plaster was not recommended for at least four days after excision lest gas gangrene and tetanus infection be undetected.[541]

[Would not prophylactic tetanus antitoxin and chemotherapy be adequate protection against such infections?—Ed.]

Gonorrheal Arthritis and Gonorrheal "Rheumatism"

Incidence. In the United States navy gonorrhea still holds first place as a cause of sick days in hospital, equaling 100,000 per year.[589] Within six years the annual rate has fallen from 85 to 44 cases per 1000 men. Arthritis occurred in about 2 per cent of these cases.[589] The greatest factor in producing this improvement has been the realization of the feeble worth of chemical prophylaxis ("little more than a superfluous ritual, something like the use of a finger bowl at the conclusion of a dinner") and substitution of rubber prophylaxis which is almost 100 per cent effective.

Rosenthal and Weinstein urged more energetic campaigns, using epidemiologic methods, in cases of juvenile gonorrhea.

Clinical Data. There were many reports on gonorrhea and its complications.[190, 311, 344, 382, 405, 431, 645]

Gonococcal tenosynovitis of flexor tendons of hands is more common than was supposed. The gonococcus was responsible for a third of the cases of tenosynovitis seen by Hamlin and Sarris. Absence of a history of trauma in a case of gonorrhea, in which signs and symptoms of tenosynovitis appear less severe than the duration of the disease would suggest, should lead one to suspect its gonococcal nature. A positive smear or culture of pus obtained by aspiration confirms the diagnosis. If aspiration yields insufficient pus, incision with primary closure is recommended.

Diagnosis. No new data on the diagnosis of gonorrheal arthritis were noted.

Blankenhorn warned against mistaking gonococcal arthritis for rheumatic fever and reported the case of a 14 year old negress to illustrate the point. Marked im-

provement resulted after three days of sulfanilamide; none had occurred from sodium salicylate.

[A migratory polyarthritis is common during the first week of gonorrheal arthritis. Chills, which often occur at the onset of gonorrheal arthritis, rarely occur in rheumatic fever.—Ed.]

Unusual Features and Complications. Five cases of gonococcal endocarditis with two recoveries were reported.[299, 572] Gonorrheal arthritis and meningitis with recovery were observed in a woman aged 29 years, by Steiner.

[It seems very probable that this was a case of gonococcal meningitis. To date, only 10 such cases, meeting rigid diagnostic requirements, have been reported; arthritis occurred in seven of the 10 cases.—Ed.]

Norbury reported what he considered to be a case of gonorrheal myelitis. Keratodermia blennorrhagicum was differentiated from psoriasis arthropathica by Epstein whose material consisted of 75 cases of keratodermia blennorrhagicum and 33 cases of psoriasis arthropathica, most of which were gleaned from the literature. The chief distinctions were: (1) the obviously different etiology, (2) the presence of silver scaling lesions in psoriasis, and of pustular keratotic lesions in keratodermia blennorrhagicum, (3) the different site of the lesions, usually soles, palms and penis in keratodermia blennorrhagicum, the extensor surfaces and scalp [and nails—Ed.] in psoriasis arthropathica, and (4) pitting of nails which rarely occurs in keratodermia blennorrhagicum.

[As the author admitted, these two diseases should rarely be mistaken for one another. This paper suffered from the lack of large first-hand observations, which are necessary to make a report authoritative. Failure to state what type of cases were included under the term "psoriasis arthropathica," further weakened it.—Ed.]

Pathology. No new data were presented.

Roentgenograms. No new studies were reported.

Laboratory Data. 1. Identification of Gonococci in Smears. Microscopic examination of smears containing only a few gram-negative intracellular diplococci is greatly facilitated if smears are first treated with 20 per cent trichloracetic acid (in lieu of heat fixation)[169]; this increases the transparency of mucus and cells, and thus renders the recognition of single pairs of gram-negative intracellular cocci much easier. Walton[795] recommended the modification of the Pappenheim-Saathof formula, by substituting absolute methyl alcohol for 95 per cent ethyl alcohol; this makes for better stability of the methyl green and better differentiation.

[The author admitted: "This stain is not selective for the gonococcus but for the Neisseria group of micro-organisms." The employment of Cohn's[169] modification of the Gram stain will result in fewer diagnostic errors than Walton's method.—Ed.]

2. Cultures of Gonococci. The cultural method (McLeod, 1934; Carpenter, 1937) is the most reliable diagnostic procedure in gonococcal infections. Malcolm and Dolman studied 5391 cultures and corresponding smears from patients with possible residual gonococcal infections. The cultural method uncovered five times as many positive and suspicious cases as did the smear technic, and 648 definitely or possibly infected persons were prevented from being discharged as cured. In one case positive or suspicious cultures were obtained on 13 occasions in 10 months, yet the corresponding smears were negative. Cultures were superior to smears in cases of chronic gonorrhea, but not in acute gonorrhea, according to Winer and Leibovitz. [Many studies indicate the necessity of cultural methods for diagnosis and establishment of cure. Failure to employ this method routinely accounts in part for the unchanged incidence of gonococcal infections in the general population.—Ed.] Most workers employ McLeod's technic (1934) with or without slight modifications. Certain charcoal prepara-

tions (blood or sugar charcoal heated to 1000° C. for one hour, graphite) added to nutrient agar were claimed to enhance the growth of gonococci, especially if the culture is incubated under 1.5 to 5.0 per cent carbon dioxide tension.[320] [This observation was first made by Pelouze, 1931. In most cases this medium is inferior to blood agar.—Ed.]. Cohn noted that gonococci rarely hemolyze a 5 per cent horse blood agar plate, whereas meningococci do after 48 hours' incubation at 37° C.

3. Gonococcal Complement Fixation Tests. Cohn [170] studied 59 proved cases of gonorrhea for a year or more to evaluate the gonococcal complement fixation test on patients treated with sulfanilamide. This drug does not affect the specificity of the test (in some cases positive and in others negative gonococcal complement fixations developed under treatment). In 11 cases reactions were negative throughout the disease. This lack of immunologic response occurred because of either the superficiality or short duration of the infection, prevention of its spread by sulfanilamide, or weak reactivity between tissues and organisms. In nine cases of persistent clinical signs and presumably a latent focus, the fixation test was strongly positive during the period of observation. In 21 cases in which clinical and bacteriologic cure resulted, there was serologic reversal from strongly positive to negative reactions. Although patients who responded bacteriologically to sulfanilamide did so in three to five days, the serologic reversal occurred an average of four months (17 days to seven months) later. If the fixation test was weakly positive, reversal was more rapid. Cohn concluded that prompt reversal of the fixation test from positive to negative can be used as a criterion of cure, but it should not supersede clinical or bacteriologic evidence of cure. If fixation tests are positive for over five months, additional clinical and bacteriologic investigations are indicated. Negative fixation tests do not necessarily mean absence of gonococcal infection.

4. Skin Reactions to Gonococcus Bouillon Filtrates. The Corbus-Ferry bouillon filtrate when injected intradermally produced positive reactions in 96 per cent of 78 proved cases of chronic gonorrhea and no reaction in 18 per cent of 188 "cured" cases.[820] [The test is not diagnostic: false positives often occur in controls; only 32 definitely positive reactions were found in 40 of the proved cases.[820]—Ed.] Rossett isolated a carbohydrate-like substance from a medium in which gonococci were grown.

[Although this substance tended to cause stronger reactions on the skin of persons with gonorrhea than on the skin of normal persons, from the author's data we cannot conclude that the test is clinically useful or highly specific.—Ed.]

The Treatment of Gonorrheal Arthritis

The 1939 literature indicated that chemotherapy (with the sulfonamides) provides the best treatment of gonorrhea and its complications. Fever therapy and other measures generally are now used only as adjuncts to chemotherapy or as alternates when it fails.

Many reports are difficult to evaluate because of (1) failure to employ rigid standards in establishing "cures"; some physicians required, as criteria of cure, negative smears and cultures for six months after resumption of a normal life, and the use of various provocative tests; others were content with disappearance of signs and symptoms of the disease; (2) variations in methods of therapy used; (3) inadequate dosage and irregular administration of the drug given; (4) variations in adjunctive measures (restriction of fluids); and (5) use of several types of treatment, the respective merits of which have not been evaluated separately. Enthusiasm for the sulfonamide group varies greatly. Many consider it the most valuable agent ever discovered for the treatment of gonorrhea. An occasional writer [806] ad-

vocated " back to the old treatment of gonorrhea," but the basis for such a statement was not adequately given.

Before discussing the treatment of gonorrheal arthritis with the sulfonamides we will first discuss the general topic of the sulfonamides.

Sulfanilamide and Its Derivatives

Literature pertaining to the sulfonamide drugs continues to be voluminous. Useful reviews on sulfanilamide and sulfapyridine appeared.[72, 105, 148, 441, 495, 496, 517, 620, 625] In their excellent review Bigler and Haralambie discussed the use of these drugs for children. Having described the mode of action, toxic and therapeutic effects of the sulfonamide drugs in detail in recent Reviews, we shall refer only to reports giving additional information. The drugs most commonly employed are sulfanilamide, sulfapyridine, and sulfathiazole, although experiences with sulfanilyl dimethyl sulfanilamide (uliron, uleron) sulfanilyl sulfanilamide (disulon), benzyl-sulfanilamide (septazine, soluseptazine and proseptasine), prontosil and neoprontosil continue to be recorded. Because sulfathiazole is a less toxic drug it probably will be used more often in the future if it proves to be as effective as sulfanilamide and sulfapyridine.

Mode of Action. Many workers[83, 281, 442, 497, 509, 556, 600, 718] agreed that these drugs exert a bacteriostatic effect on susceptible organisms, but the mode of action is not yet known. Locke and co-workers[5, 492] suggested that sulfanilamide depended on its anticatalase effect. This hypothesis did not seem tenable to MacLeod.

Other studies on the mode of action of the sulfonamides appeared.[281, 718, 724] From these reports it is apparent that the bacteriostatic effect of the sulfonamide drugs is probably dependent on interference with the nutrition of microörganisms.

Studies were made suggesting that sulfathiazole is as effective as sulfapyridine in the treatment of experimental meningococcal and pneumococcal infections[527] and that sulfapyridine is superior to sulfanilamide in the control of other experimental infections.[495]

Absorption, Diffusion and Excretion. The absorption, distribution and excretion of various sulfonamides were studied by Brown, Thornton and Wilson, Daniel and Farrell.

Toxic Reactions. Some physicians hesitate to use sulfanilamide or its derivatives because of the possible toxic effects. This attitude is hardly justified; extensive use has proved that these drugs if intelligently administered can be employed with much greater impunity than has hitherto been considered possible. Because their toxic effects were discussed in detail in previous Reviews, this year's analysis will only consider the more serious ones and the particular drug which is most likely to produce them.

No new toxic reactions were observed.[73, 103, 105, 301, 441, 497] Van Dyke, Greep, Rake and McKee concluded from experiments on animals that sulfapyridine is definitely more toxic than sulfathiazole; the principal pathologic change was renal damage. Studies indicated that sulfathiazole is more rapidly metabolized and undergoes much less conjugation than sulfapyridine.

Minor reactions (see previous Reviews), although frequently observed, do not contraindicate continued use of sulfonamide compounds. Of the more serious complications, granulocytopenia and agranulocytosis are most frequently encountered. They may result from either sulfanilamide or sulfapyridine. They have not been

observed from sulfathiazole. Of five patients with agranulocytosis [199, 562, 689, 741] from sulfapyridine one died [562]; another [199] had an associated angina. Additional cases attributable to sulfanilamide were reported [192, 301, 351, 516]; death ensued in one instance.[192] A significant decrease in the leukocyte count may occur from small doses given over a short time, although in most cases granulocytopenia followed the administration of large doses for long periods. This complication may not develop until days after the drug has been discontinued.[562] If it appears during therapy, the drug should be withdrawn and excess fluids given. Pentnucleotide and liver extract have not been proved effective, for death occurred despite their use.

[Long and his associates [498] concluded that when agranulocytosis occurs during therapy the prognosis is good if the toxic reaction is recognized at its inception. This can be assured only by making frequent blood counts.—Ed.]

Hematuria with renal and ureteral pain and nitrogen retention occurred during sulfapyridine therapy [600, 714]; they disappeared promptly when the drug was stopped and extra fluids were given. Oliguria, anuria and azotemia have been observed only from sulfapyridine and sulfathiazole. Anuria is probably due to deposition of acetylsulfapyridine and acetylsulfathiazole crystals in renal tubules, occasionally to blocking of ureters and renal pelves by calculi of these two salts.

Acute hemolytic anemia occurred thrice as often from sulfanilamide as from sulfapyridine. Acute hemolytic anemia from sulfathiazole has not been reported. Koletsky observed hemolytic anemia on the third day of sulfanilamide treatment. The erythrocyte count began to decrease on the second day of therapy and continued to decrease until death on the fifth day. Necropsy revealed erythropoietic hyperplasia of bone marrow, iron pigmentation of liver and spleen, and pallor of viscera. Koletsky pointed out that both his and Woods' (1938) patient had syphilis.

Peripheral neuritis, a rare complication, can result from any of the three commonly employed sulfonamide compounds, although it occurs less frequently from sulfanilamide than from sulfapyridine or sulfathiazole; another case was reported.[797]

[Similar complications have occurred more often with sulfamethylthiazole, sulfanilyl sulfanilamide and sulfanilyl dimethyl sulfanilamide.—Ed.]

Cyanosis. Measurements of functioning and nonfunctioning hemoglobin were made [73] on the blood of nine patients given sulfanilamide in an attempt to relate them to the degree of clinical cyanosis. Correlation was not possible; the cause of cyanosis on treatment with sulfanilamide is not established. [Cyanosis observed during sulfanilamide therapy is not due solely to sulfhemoglobinemia or methemoglobinemia.—Ed.] But Wendel generally demonstrated methemoglobin in blood, both spectrophotometrically and by the Van Slyke method, during sulfanilamide therapy. Cyanosis disappeared when 0.1 to 0.2 c.c. of a 1 per cent solution of methylene blue was administered orally each day. [Wendel's idea that methemoglobin is the best explanation of the cyanosis is at variance with the conclusions of Biglow and Werner and others.—Ed.] Cyanosis is less marked with administration of sulfapyridine and minimal with sulfathiazole.

Summary. Those interested in the relative toxicity of the sulfonamides most commonly used should consult a recent article by Long and coworkers.[498]

All toxic reactions except leukopenia and agranulocytosis can be recognized by careful clinical examination. Whenever possible, every necessary laboratory method should be used during treatment. Total and differential leukocyte counts, determinations of hemoglobin and examination of urine should be done regularly. Pallor, icterus and rashes are readily detected. Increase in symptoms or appearance of fever are often important warning signals. The urinary output of patients receiving sulfapyridine and sulfathiazole should be recorded to detect the oliguria which can herald approaching anuria. A fresh specimen of urine should be examined daily for erythrocytes whenever oliguria occurs. If a patient has had a serious toxic reaction, he

is likely to have an earlier and more severe reaction if the drug is administered again. If its second administration is indicated, a test dose of 5 grains should be given. If no reaction ensues in 12 hours, the physician may proceed watchfully with another course of therapy in which the doses are increased gradually. With the appearance of moderately severe toxic effects, administration of the drug should be continued with caution and stopped if reactions become severe; then extra fluids should be given. No new data on the prevention of toxic reactions or on contraindications to the use of the sulfonamide compounds were reported.

Treatment of Gonorrheal Arthritis with Sulfanilamide

Only four papers [133, 168, 443, 827] dealt specifically with the treatment of gonorrheal arthritis with sulfanilamide. Except for Caldwell's report results were similar to those reported last year.[6] Keefer and Rantz divided 14 cases into three groups: (1) those of infected synovial fluid; (2) those of sterile synovial fluid, and (3) those without effusions. They gave 4 to 5 gm. of the drug daily. Best results were obtained in group 1 (five cases): infected fluids were sterilized in three to seven days; despite this, damage to synovial membrane apparently delayed clinical recovery (these patients averaged the longest hospital stay). The four patients in group 2 recovered without articular disability or deformity. Treatment required an average stay in the hospital of 30 days in group 3 (five patients), as compared to 50 days in a similar hospitalized group in which older methods of treatment were used. The arthritis recurred twice after withdrawal of the drug in one case and once in another, but re-administration of the drug was effective each time. Keefer and Rantz noted (1) that concentrations of the drug were about equal in synovial fluid and blood, (2) that often, but not always, the local focus was clinically and culturally cured, (3) that synovial fluid cell counts diminished and fluid accumulated less rapidly with the use of sulfanilamide than with other remedies, and (4) that sulfanilamide did not hinder formation of immune bodies. This hypothesis that the normal immune mechanism must come into play for permanent cure was not substantiated by the work of others.[168, 170]

Coggeshall and Bauer,[52, 168] using larger doses, noted within 48 to 72 hours, striking clinical improvement in nine of 14 proved cases, and in two of four probable cases of gonorrheal arthritis. These results were more prompt and satisfactory than those from any other therapy. They further noted (1) sterilization of infected synovial fluids in 48 to 72 hours, (2) cure of the local focus in 17 of the 18 cases, (3) failure of gonococcal complement fixation tests to become positive on three patients with infected synovial fluids who responded promptly (48 to 72 hours) to sulfanilamide, and (4) the largest percentage of cures when the level of sulfanilamide in the blood was 10 mg. per cent or higher.

Caldwell, using moderate (20 grains every four hours) and small (60 grains daily) doses of the drug in eight cases of gonorrheal arthritis, observed rapid subsidence of joint symptoms in five, gradual subsidence in one,

and slight improvement in two. To hasten resolution he splinted affected joints.

[The latter procedure is regarded as of more value by him than by us. We consider incorrect his statement that "simple sterilization of the synovial fluid by use of sulfanilamide will not eliminate the factors making for destruction of the cartilage." Larger doses of the drug, control of fluid intake and determination of concentrations of sulfanilamide in blood would probably have given him better results.—Ed.]

Prompt relief from sulfanilamide was noted in Yandell's case of gonorrheal arthritis. Spink and Flink cured seven cases therewith. Silver and Elliott noted one patient with gonorrheal arthritis who "responded well" to sulfanilamide (details not given) but of 23 such patients previously given the drug only eight were relieved. Seven of the 10 patients treated by Waugh and Dawber with moderate doses of the drug were relieved.

Five cases of gonorrheal tenosynovitis were treated with sulfanilamide, immobilization and heat[362]; the associated arthritis of wrist (two cases) and conjunctivitis (one case) subsided "rapidly." Results were "good"; in only two of the cases did slight flexion contractures occur.

The literature of the past three years indicates that best results have been obtained in the treatment of gonorrhea and gonorrheal arthritis when large doses were given at regular intervals, day and night. The fluid intake should be kept constant (2,000 c.c.) and a blood level of 10 to 15 mg. per cent should be maintained. Under these conditions, obvious improvement should begin within 48 to 96 hours.[168, 443, 591] If it does not, the case is probably "sulfanilamide-resistant" and will require some other form of therapy (alone or in conjunction with sulfanilamide).

Many physicians have been unwilling to treat gonorrhea with sulfanilamide alone, but also have used locally the time-honored chemical agents. But it is difficult to conclude that such combined therapy is superior to sulfanilamide alone. Still others used sulfanilamide, vaccines and local treatment. Better controlled studies will give us the final answer.

[Current studies are making much of the foregoing work outmoded. Many workers now recommend sulfapyridine or sulfathiazole to the exclusion of sulfanilamide. —Ed.]

Treatment of Gonorrhea and of Gonorrheal Arthritis with Sulfapyridine

Gonorrheal Arthritis. Reports concerned specifically with the treatment of gonorrheal arthritis with sulfapyridine did not appear in the literature reviewed. Certain workers[168, 491] advocated its use in sulfanilamide-resistant cases.

Urogenital Gonorrhea. The literature pertaining to its use in the treatment of gonorrhea has increased greatly. The data thus far presented indicate that sulfapyridine is superior to sulfanilamide in the treatment of gonorrhea and its complications. This may be due in part to the fact that patients treated with sulfapyridine received more nearly full doses than did those receiving sulfanilamide.

Treatment of Gonorrhea with Other Sulfonamide Compounds

Results with the following drugs were reported in cases of gonorrhea but not of gonorrheal arthritis. Results with sulfanilyl dimethyl sulfanilamide (uliron, uleron) varied greatly. Peripheral neuritis was a serious and not uncommon effect of this drug and also of sulfanilyl sulfanilamide (disulon); hence many workers discontinued their use. So little data on the value of benzyl-sulfanilamide (proseptasine, septazine and soluseptazine) were reported that an evaluation of it cannot yet be made.

Fever Therapy for Gonorrheal Arthritis

In view of the value of the sulfonamides fever therapy continues to play a subordinate rôle. Only Beach considered it "more certain" than sulfanilamide; other writers recommend it only in cases resistant to chemotherapy. A few reports concerned the effect of fever therapy alone: "cures" were obtained in from 25 to 70 per cent; little or no relief resulted in 10 to 30 per cent of the cases; in the rest improvement was moderate to marked. Fever sessions were usually for five to eight hours at 106 to 107° F. Failures were due to inadequate heating or to residual damage present prior to hyperpyrexia.

None of Gwynn's 76 patients were cured; 80 per cent were markedly relieved. Notable improvement occurred in 73 per cent of Ferderber's 77 cases. Davison, Lowance and Crowe treated 25 patients; 24 per cent were cured, 52 per cent notably benefited, 24 per cent not relieved. Of the 50 patients treated by Johnson and Whiston 88 per cent were markedly or moderately relieved, 12 per cent were not. Bierman and Levenson gave "short fever sessions" (six to eight hours) to 16 patients, seven of whom were cured; long sessions (10 to 12 hours) to 24, 16 of whom were cured. In 54 per cent of Ledbetter's 15 cases cure was obtained; in 33 per cent notable relief. [The average fever session was only three hours at 106° F., an amount often insufficient.—Ed.] Of Bromberg's 40 patients, 80 per cent were cured. Cures were "expected" in 70 per cent by Cheetham; 90 per cent of Neymann's patients (unstated number) were cured or markedly relieved. Vassiliadis reported cures in four cases and Gottesman in 12 of 14.

Reactions to fever therapy were few: temporary respiratory collapse occurred in two cases and neuronitis in five,[219] shock in three of 300 cases[152] and death in one case (no details).[269] The proper technic of fever therapy was again described.[71, 253, 269, 274, 479] Ishmael favored the use of fever therapy plus autohemotherapy.

Fever Therapy Combined with Sulfanilamide for Gonorrheal Arthritis

Several physicians considered the combined use of fever therapy with chemotherapy better than either alone and recommended this combination in cases of sulfanilamide-resistant gonorrheal arthritis.[42, 71, 253, 274, 549, 558, 578] The combination was said to be successful in from 90[42] to almost 100 per cent[578] of cases resistant to either alone. Some writers[578] used sulfanilamide for three or four days prior to one 10-hour fever session. Others[274] gave

5 gm. of sulfanilamide daily for two days, then six or eight hours of fever (106.4° F.); of 14 patients so treated 11 were cured. According to Muether and Andrews, fever produced by typhoid vaccine ("more economical than that from machines") plus the use of neoprontosil reduced the stay in the hospital in eight cases of gonorrheal arthritis by "about 50 per cent."

[Details in most of these reports were meager; the number of patients treated was small, the control material inadequate for a final appraisal of combined therapy. Further studies thereon are to be desired.—Ed.]

Fever therapy does not alter the concentration of sulfanilamide in blood except as it slows intestinal absorption of the drug. Sulfanilamide with fever therapy does not increase the hazards of the latter.[484]

Other Remedial Agents for Gonorrhea and Its Complications

Corbus and Corbus again advocated the use of the Corbus-Ferry bouillon filtrate in the treatment of gonorrhea and its complications. Chrysotherapy did not produce benefit in four cases of gonorrheal arthritis.[452]

Fever Therapy: General Discussion

Methods. The development of artificial fever and methods for its production were discussed.[102, 274, 314, 331, 466, 469, 473, 474, 558, 587, 597, 644, 709] Results and hazards were considered about equal, whether fever was produced by the induction method, by hot moist air or by hot sprays of water. Many workers [42, 71, 473, 578] favored 10 to 12 hour fever sessions, especially in gonococcal infections, either with or without sulfanilamide and with additional local pelvic heating.[70]

Preparation of Patient and Management during Fever. Those who use fever therapy are referred to several reports on the preparation of patients for fever treatments [455, 473, 474, 479, 597, 658] and on their management during fever.[107, 294]

Complications, Untoward Results. Careful selection and management of patients during fever sessions has made the procedure relatively safe. Minor reactions (headache, nausea, vomiting, tetany, muscle cramps, herpes labialis) were common.[474, 479, 559] Serious reactions like neuronitis [219] and other neurologic changes, some of which were transient, some permanent,[181] were rare. Three deaths from fever therapy occurred.[269, 314, 486] The parenchymatous, necrotic, hemorrhagic and congestive changes that can affect tissues, especially the liver, from overdoses of fever were studied.[348, 817]

Tuberculous Arthritis: General Comment

Incidence. The incidence of tuberculous arthritis is still decreasing. The recent admission rate for osseous tuberculosis per 1,000 admissions was 1.58 in the Charity Hospital, New Orleans, 2.27 in the El Paso City-County Hospital.[95] In a New York hospital fusion operations on tuberculous knees have decreased in number to a third of that 10 years ago.[772]

Clinical Data. New cases of tuberculous arthritis were reported: knees were affected in 222 [772] and in 47 cases,[528] spine, hips or knees in 71,[95] and various joints in 310.[160] Trauma preceded articular symptoms in only 37 per cent of Toumey's cases. The incidence of pulmonary tuberculosis in cases of tuberculous arthritis has varied in different series from about 10 to 70 per cent; it was 20 per cent in that of Breck and Basom. The disease usually affects children; of Le Cocq's patients 85 per cent were children less than 10 years of age. Blood proteins are only slightly altered.[671]

Diagnosis. Early specific diagnostic signs may be absent.[672] Roentgenograms in early stages of the disease are quite nonspecific,[772] but when roentgenograms reveal swelling of soft tissue, haziness of detail, preservation of joint space and localized bone atrophy, tuberculosis should be considered.[426] Mantoux tests are usually positive but may be negative even in proved cases of tuberculous arthritis.[672] Of greatest value for early diagnosis are biopsy of synovial membrane and aspiration of fluid for guinea-pig tests. Both should be done; one may be positive, the other negative.[772] In 82 per cent of Toumey's cases (knees), biopsies revealed tubercles; frozen sections are inferior to permanent sections. Since biopsy of a joint is not without danger Seddon recommended biopsy of inguinal glands on the same side as the affected knee. Tuberculous inguinal adenitis does not exist as an isolated disease. In 15 (80 per cent) of 18 proved cases of tuberculous knees, biopsies of inguinal glands revealed tuberculous adenitis either by section or guinea-pig test or both; they were negative for tuberculosis in only three cases. Although a "negative biopsy" of inguinal nodes does not exclude tuberculous arthritis in an adjacent arthritic knee, a "positive test" is strong and reasonably accurate presumptive evidence.

Treatment. The current tendency is to treat children conservatively at least for awhile,[679] but to treat adults surgically by some fusion operation, except that one may temporize for awhile when an upper extremity is affected.[95] Cleveland's statistics prove again that the disease is serious and the mortality high. Operation alone will not effect a cure but may turn the tide in favor of the patient. End results depend on the type and extent of the infection. The mortality noted by Cleveland was 48 per cent among patients with pulmonary tuberculosis and positive sputum, or pulmonary tuberculosis, negative sputum and metastatic disease, 10 per cent among those without pulmonary disease, or with pneumonitis, negative sputa and no metastatic disease (aside from joints).

[Fusions should be done, not during the acute progressive stage, but only when the articular lesion has become relatively quiescent through immobilization.—Ed.]

Tuberculous Arthritis: Special Localizations

Joints affected are, in order of frequency, spine, hips and knees[95, 478]: of the 330 affected joints in Cleveland's 310 cases 95 per cent were weight-bearing joints.

Spine. Early diagnosis of spinal tuberculosis presents many difficulties.[89] The details of Cleveland's 173 cases of tuberculous spondylitis were given: any vertebra, but especially the seventh thoracic to the fourth lumbar vertebrae, were affected.

Tuberculous spondylitis may roentgenographically simulate malignancy, nonspecific infections, lymphogranuloma inguinale, congenital or traumatic lesions, but especially well-encapsulated and localized suppurative spondylitis from staphylococci or streptococci of low virulence. One patient [287] presented what could only be considered traumatic spondylitis until the premortem appearance of tuberculous meningitis and miliary tuberculosis a year later. In a case of apparent spinal malignancy spontaneous fractures developed from tuberculosis in 14 ribs, as well as the spine.[366] In a case of Pott's disease earliest symptoms were those of tuberculous "meningitis sympathica"; tuberculous spondylitis was discovered months later.[698]

"Having seen all cases under conservative treatment go on to deformity, dependency and destruction" Bosworth strongly recommended in all cases a Hibbs' fusion operation reinforced by long iliac grafts, to be done as early as possible. But others [705, 746] were pessimistic about results of surgical treatment. Such treatment prevents collapse but results are "not satisfactory." Partial fusion generally results, but not "complete bony fusion," hence the disease too often progresses. A good "class A" result was obtained after fusion in only 12 of Smith's [705] 49 cases. Results of fusion were excellent in 54 per cent of Cleveland's cases.

Hips. When hips are affected, multiple foci, often too small to be seen in roentgenograms, are usually present. Among Cholmeley's 55 children the commonest foci were in the mesial and lateral half of the acetabular roof and in the femoral neck. To detect them serial roentgenograms were taken in different planes. Farkas devised a new operation to provide more complete immobilization. Albee and Shands favored extra-articular fusion by tibial grafts rather than intra-articular fusion.

Knees. London practitioners are now (correctly) suspecting tuberculous arthritis of knees early, long before the classical picture appears, often too early for roentgenograms to support the diagnosis.[672] Differentiation in early cases must be made from gonorrheal and atrophic arthritis.[772] After several months to a year of illness roentgenographic diagnosis becomes more certain, but in 32 of Toumey's long standing cases no clinical or laboratory proof of tuberculosis was obtained until operation. Although they approve of "radical" (i.e., surgical) treatment of tuberculous knees in adults, many orthopedists avoid operations on children under 15 years so as not to interfere with bone growth or produce shortening of legs. But McKeever and Toumey considered such conservatism faulty. After an average of three years of conservative treatment given to McKeever's 47 juvenile patients, the disease was still active in every affected knee. His statistical results from "economical resection" to produce femoro-tibial synostosis were su-

perior. Among Toumey's 222 cases in which fusions were done, solid fusion resulted in 196. Results of fusion were "excellent" in 54 per cent of Cleveland's 57 cases.

Other Sites. Tuberculous tendinitis and bursitis are uncommon: three cases affecting hands were reported.[603]

Osteitis Tuberculosa Multiplex Cystica. This disease, first described by Jungling (1920), generally affects small joints; only Elliott (1935) has previously reported involvement of large joints (two cases in knees). In one case a knee and elbow were proved to be tuberculous at the time of fusion; over 10 years later, when seen by Warner multiple tuberculous cysts had developed in the firmly ankylosed knee and elbow.

"Tuberculous Rheumatism." No reports of this supposed [but very doubtful—Ed.] entity appeared.

Pneumococcal Arthritis

With the advent of highly effective chemotherapy against pneumococci, pneumococcal arthritis appears to be diminishing almost to the vanishing point. No cases were reported in the literature for the year. Shaffer and Bennett in an experimental study on rabbits, reported that virulent pneumococci, type III, when injected intravenously, rapidly gained access to joints and within 24 hours nearly all animals had involvement of one or more joints. Cocci were demonstrated in joints when blood and other organs were sterile. They attributed the localization of so-called arthropathic strains of bacteria to the small amount of tissue intervening between the blood vessels and the joint cavities.

[Many reports on the successful chemotherapy of pneumococcal infections with sulfapyridine appeared. But since then a new agent, sulfathiazole, has been extensively used against pneumococcal infections; it appears to be as effective as sulfapyridine and its toxicity is considerably less.—Ed.]

Syphilitic Arthritis and Synovitis; Charcot (Tabetic) Joints

Syphilitic Arthritis. Syphilitic arthralgias may characterize earlier phases of syphilis; syphilitic arthritis is usually a tertiary lesion (Jostes and Roche). But a mild arthritis "of minor significance" may occur in the secondary stage, and hydrarthrosis may recur during the entire course of syphilis. During the secondary stage "the joint may be invaded secondarily from a neighboring periostitis, osteitis or osteomyelitis." A common late arthritic involvement is chronic synovitis with periarticular thickening and synovial hyperplasia; chronic hydrops may occur. Gummatous osteo-arthritis may involve larger joints, e.g., knees, and cause articular enlargement with tense, shiny skin but no inflammation or impairment of mobility. Ankylosis does not occur unless secondary infection intervenes. Blood proteins were only slightly altered in five cases of syphilitic arthritis.[671]

Charcot Joints. The etiology, pathology and symptomatology of these

lesions were discussed.[309, 521, 685] Sherwood and Hutchins reported 15 cases and summarized data on 586 cases from the literature. From 5 to 10 per cent of tabetics develop Charcot joints; multiple joints are affected in a third of cases. Joints are not always painless; Wassermann reactions may be negative in both blood and spinal fluid even when the condition is unquestionably due to tabes dorsalis. The speed of development was stressed by Chitty who reported a case in which the first roentgenograms of the hip were negative but five months later there was complete disappearance of the femoral head.

Current writers advocated arthrodesis. McCauley obtained solid fusion in six of seven cases, Cleveland in five of seven cases, and Giannestras in eight of 10 cases reported by him and in 40 of 46 cases culled from the literature. Several writers urged care in selecting cases for arthrodesis, and recommended operation only when disintegration is not too far advanced. In advanced cases and those in which the neurologic disturbance itself produces crippling, arthrodesis is likely to result in failure; hence they recommended instead external support by means of braces. Although antisyphilitic therapy will not halt the articular process it should always be instituted.

Brucellosis: Undulant (Malta) Fever

Incidence. The incidence of brucellosis is increasing. The 2,675 cases noted in 1937 probably represent only a fraction of those which occurred.[259] Thirty-eight reports concerned its widespread appearance in the United States, Canada, Iraq,[55] Jerusalem,[456] and South Africa. "Ditch fever" in Arizona is said to be brucellosis.[185] Acute brucellosis is two or three times as common among males as among females; latent brucellosis affects the sexes equally. The disease is commoner in small towns and rural districts where raw milk is often used. Humans are more susceptible to porcine and caprine strains than to the bovine.[688] The former produce more severe disease. Porcine strains may affect horses, poultry, dogs and cows; less commonly sheep, mules, rabbits. The disease is commoner in summer: animals are more infectious when calving, and raw milk is a better culture medium in hot weather. Mosquitoes can, but rarely do, transmit the disease.

Clinical Data. The protean manifestations of the disease were described.[37, 109, 131, 158, 232, 632, 688, 821] The disease must be looked for: mild acute cases often masquerade as "flu," chronic cases as "neurasthenia." A list of 166 symptoms and signs attributed to brucellosis was given.[523] Calder compared the symptoms in his 550 cases to those in Hardy's (1936) series.

Symptoms Referable to Muscles and Joints. Current reports[131, 259, 633, 704] indicate that arthralgia is common (normal looking joints may be "excruciatingly painful") [259] but arthritis is rare. In one case the disease simulated atrophic arthritis.[633] In another it was "indistinguishable from rheumatic fever" but "yielded dramatically to convalescent antiserum" [704]; in two cases hydrarthrosis of knees was present.[704] Articular effusions occurred in 15 per cent of Strachan's (1932) 268 cases in South Africa; the spine was often affected. Bishop noted one case of spinal involvement:

endosteal and periosteal reactions with resulting sclerosis of vertebral bodies and spur formation. McGinty and Gambrell stated that in the first reported cases undulant fever was regarded as chronic rheumatism (Curry, 1901).

Pathology. The histology of cutaneous reactions to *Brucella melitensis* antigen was described,[305] also details of necropsies in two fatal cases.[588, 609] In one case the disease resembled Hodgkin's disease.[588]

Diagnosis. This is difficult and depends largely on laboratory tests, the exact interpretation of which is impossible.[530] Tests used are (1) cultures of body fluids, namely blood, urine, stools, bile, spinal or synovial fluid, (2) animal inoculation, (3) agglutination tests, (4) intradermal tests with brucellergin, (5) opsonocytophagic test.

Cultures. When positive, cultures give the most reliable evidence. By their special method cultures were positive in five of seven cases of Smith and Poston, but sometimes cultures take 17 days. Cultures have been positive when other tests were negative, but negative cultures do not exclude the disease.[259, 260, 456] A new culture method was described.[456]

Agglutination Tests. Their significance and interpretation remain as given in our last Review.[23, 259, 531, 683, 688, 704, 821] A positive test is suggestive; the test is negative in 20 to 30 per cent of acute cases of brucellosis, usually negative in chronic cases and positive in 10 per cent of "normal" persons.

Skin Tests. Skin tests with killed organisms were considered reliable by some,[109, 632] unreliable by others[131, 284, 523] who preferred intracutaneous tests with Foshay's antiserum ("positive" in 92 per cent of 24 acute cases, 91 per cent of 541 chronic cases of "probable brucellosis"). Many of the "reactors" in school children and college students, and in adults and children with vague chronic disabilities may have unsuspected chronic brucellosis.[23, 530, 633]

Opsonocytophagic Reaction. This was considered reliable by some,[131] of limited value by others.[260]

Therapeutic Test. If brucellosis is present, sulfanilamide will cause a favorable response and the opsonocytophagic activity for brucellae will rise, according to Blumgart and Gilligan.

[Results from sulfanilamide are not always successful.—Ed.]

Conclusions on Laboratory Tests. One test alone is of little value; data from several tests may be valuable; if agglutination, skin and opsonocytophagic tests all give positive reactions, the evidence is nearly specific.[131] A positive test by even one method occurs 10 times as often in cases of brucellosis as among normals; positive reactions to two or more different tests occur 70 times as often among patients with symptoms compatible with brucellosis as among controls. But it is discouraging to find such tests negative "when they should be positive."

Blood Counts. A characteristic blood picture "found in no other disease" was noted by Calder and associates in more than 50 per cent of 300 cases of brucellosis: leukopenia, lymphocytogenesis and a lymphocytic "shift to the left"; monocytes were not increased, monocyte-lymphocyte ratios were low. Munger and Huddleson noted leukopenia with relative lymphocytosis, monocytosis, basophilia of neutrophilic granules and "liver damage cells."

Treatment of Brucellosis

Since the disease tends to be self-limited it is difficult to evaluate various remedies. Treatment is more successful in acute than in chronic cases.[523]

Serums and Vaccines. Three of five patients were cured by a "specific polyvalent serum."[284] Brucellin provokes specific immunization according

to Calder; of 180 patients treated therewith 80 per cent became asymptomatic within three months. Smith and Poston preferred immune human serum for acute cases with positive blood cultures and no antibodies, Brucella vaccine for others.

Fever Therapy. Of 15 patients given fever therapy (three sessions of five hours each, 105 to 106° F. rectal) 80 per cent were "greatly improved" although this amount of fever will not kill Brucella organisms in vitro.[253, 475]

Chemotherapy. In 1939 physicians evaluated sulfanilamide for brucellosis less optimistically than in 1938. Symptoms disappeared under sulfanilamide therapy in all of Condell's five cases, and in two other cases[46, 490] in which initial doses were about 60 grains daily for three or four days, 40 grains daily for two weeks more. (In only one of these cases were joint symptoms dominant.[185]) Results of other physicians were disappointing. Sulfanilamide in "maximum therapeutic doses" produced temporary improvement followed by recurrences in the five cases of Bynum, and in Schroeder's case. The drug influenced the bacteremia but not the clinical picture in six other cases,[456] and a case of brucellosis with endocarditis was resistant to three courses of the drug.[706]

[In some cases doses were small and not controlled by blood studies.—Ed.]

Results of this therapy seemed "most encouraging" to Blumgart and Gilligan who summarized 30 reports in the literature to date: of 74 cases recoveries were attributed to the drug in 68 (92 per cent), there were failures in six (8 per cent) but relapses occurred after recovery in 14 (20 per cent). Failures and relapses were mostly from under-treatment. "Recoveries" were rapid; symptoms left within two to 12 days. Recommended dosage was about half a grain per pound of body weight per 24 hours, divided in six doses and continued for three to four days after subsidence of fever (example: for a 150 pound man, 4 to 6 gm. or 60 to 90 grains daily); maximal dosage 6 gm. in 24 hours. Response in acute cases seemed better than in chronic cases.[821]

In guinea-pigs the melitensis variety is less responsive to sulfanilamide than are the suis and abortus varieties[153]; this may explain the poor results in the melitensis cases of Kleeberg, Gurevitch and Alkan. Sulfapyridine in large amounts had little effect on Brucella infections in guinea-pigs.[357]

The "simple, easy and successful" treatment in Ragsdale's 10 cases was intramuscular injections of sodium cacodylate, 0.45 gm. twice weekly. Kaolin was used by Thames to relieve nervous symptoms. Diets high in vitamins with vitamin supplements (B, C, nicotinic acid) were recommended.[131, 632, 821]

Prophylaxis. Elimination of reactors from herds is costly, impracticable and relatively ineffective.[232, 688, 815] Pasteurization of milk is more effective. Perhaps the population can be immunized by generalized inoculation against brucellosis and typhoid fever with a mixed heat killed vaccine effective in animals (Kolmer and Bondi). Infected humans may act as carriers; infected urines and stools should be cared for as in typhoid fever.

Typhoidal Arthritis

No reports appeared.

Meningococcic Arthritis

No reports appeared.

Suppurative (Purulent, Septic) Arthritis

General Comment. Clinical features of suppurative arthritis were reviewed.[426, 524, 743, 744] Staphylococci cause it in about 50 per cent of cases, hemolytic streptococci in about 25 per cent, miscellaneous bacteria (pneumococci, etc.) in the rest.[524] Sweetapple wrote "Synovial fluid is strongly antibacterial while fresh, but excellent pabulum for bacteria when stale. [What is stale synovial fluid?—Ed.] Surgeons have learned to trust in the antiseptic properties of the peritoneum; we are probably too chary of trusting the synovial membranes." In some cases the arthritis is mild and not frankly suppurative, in others suppurative and rapidly destructive. Among McGovern's 24 cases two arose from ear infections; one from nonhemolytic streptococci, the other from a mixed infection of pneumococci and *Staphylococcus albus.* In five cases reported hips were involved.[91]

Of Streptococcal Origin. A patient with severe hemolytic streptococcal sepsis (tonsillitis, pneumonia, nephritis, arthritis) was given sulfanilamide by Spink: function of the knee was restored completely. In synovial exudate before treatment cocci were mostly extracellular, after treatment mostly intracellular.

Of Staphylococcal Origin. A case of suppurative arthritis of knee and elbow caused by hemolytic staphylococci was used by Preston to show that the clinical course of staphylococcic arthritis differs in some respects from that produced by other pyogenic bacteria. [The differences were not made clear.—Ed.] In animals infected with "ordinary abscess producing *Staphylococcus aureus*" invasive local lesions with multiple metastatic abscesses developed; in those infected with "toxicogenic *Staphylococcus aureus*" mild, noninvasive local lesions with marked "toxic degeneration of viscera" developed.

For all such cases Preston recommended (1) aspiration of joints, (2) destruction of organisms locally by lavage with specific bacteriophages, (3) prophylaxis against multiple metastatic abscesses by the intravenous use of autogenous bacteriophage, (4) immobilization of joints, (5) destruction of the bacterial toxin by giving transfusions and ascorbic acid which inhibits the hemolytic power of staphylococcal toxin, (6) increasing the patient's general resistance by diets and fluids, (7) restoration of articular motion by physical means.

[The use of sulfapyridine and sulfathiazole may make such remedies obsolete. —Ed.]

Treatment by Surgical Measures. General principles were outlined[91, 115, 355, 743, 744] as in previous Reviews. Pyogenic infections of feet should be treated like those of hands; this necessitates a knowledge of the interrelationships of joints, tendon sheaths, bursae, etc.[115] Patients whose arthritis is not amenable to newer chemotherapeutic agents may require (1) bilateral incisions into joints (often unsuccessful), (2) lavage of joint cavity, (3) closure of joint and immobilization in plaster, or (4) drainage, traction and temporary immobilization.[744]

Reconstructive and stabilizing surgical methods used in 46 cases of residual damage from suppurative arthritis of hips were discussed by Hallock. Reconstruction operations controlled dislocation and pain but limited the motion considerably and the control of pain was not always permanent. Results of arthroplasty were better but the operation was not often possible. "Shelf stabilization operations," gave stable joints but also shortening and a limp. Fusion produced stable painless hips without a marked limp and was the operation of choice.

[Commenting on this paper Key stated: "Every reconstruction operation is a subterfuge. I have never seen one that I liked." Dickson added: "My experience with reconstruction operations and shelf operations parallels that reported. Fusion is by far the most dependable operation." In the future the situation may be improved by the use of two new procedures, chemotherapy, and the Smith-Petersen cup.—Ed.]

Arthritis of Scarlet Fever: Postscarlatinal Rheumatism

No publications appeared.

Rarer Forms of Specific Arthritis

The Arthritis of Bacillary Dysentery. A case of arthritis associated with *Bacillus dysenteriae Flexner* was reported.[40] Baker referred to 25 cases seen by Dudgeon in Macedonia. In only one of 10 cases studied bacteriologically were organisms recovered from joints; in this case the blood culture was also positive. Baker's patient was a carrier of *Bacillus dysenteriae Flexner,* and, except for a mild episode of watery diarrhea a year previously, was in excellent health. Only one similar case is reported in the literature.

The patient, a man 42 years old, first complained of severe pain in the left wrist, drenching sweats and loss of weight. Temperature varied from 101° to 103° F. Later the right wrist and hand became almost helpless because of pain, swelling and muscle spasm. Hands, wrists, elbows, knees, right shoulder and left hip became involved. Blood and joint cultures were repeatedly negative; the stool contained numerous colonies of *Bacillus dysenteriae Flexner* and the agglutination reaction in the serum reached a titer of 1:640. Roentgenograms were negative. The condition eventually cleared up. Although the etiologic factor was not definitely established, Baker felt the most probable explanation was an allergic response in joints. In such obscure cases he advocated agglutination tests.

Bilateral ankylosis of hips following dysentery (type unstated) was treated successfully by capsulectomy.[794]

Arthritis Associated with Lymphogranuloma Venereum. Arthritis may occur with lymphogranuloma venereum, as noted by Frei (1938) and by Hellerstrom (1929). Two reports on this subject appeared.[220, 824]

Dawson and Boots reported 24 cases: 1. The arthritis pursues a variable course but usually appears in a chronic, indolent, serous form with a marked tendency to relapse. Intermittent hydrarthrosis is not uncommon. Occasionally joints are acutely swollen, painful and tender. 2. The arthritis is usually polyarticular and has a predilection for knees, ankles and wrists; frequently both knees or both ankles are involved simultaneously. 3. The arthritis persists for weeks or months, but in the cases observed, there was no obvious destruction of bone or cartilage. Except for periarticular swelling and effusion within the joint, roentgenograms revealed no changes. 4. The character of the synovial fluid varied considerably but it was never purulent. 5. Cultures of synovial fluid on common bacteriologic media were sterile. 6. In all cases the Frei reaction was positive and in most cases other evidence of infection with lymphogranuloma venereum was present. Dawson and Boots attempted to demonstrate both the virus and Frei antigen in aspirated synovial fluid; results were inconclusive.

Wright and Logan described osseous changes with lymphogranuloma venereum. Their diagnostic criteria were as follows: (1) clinical symptoms should be those of lymphogranuloma venereum; (2) Frei reaction should be positive; (3) pathologic, bacteriologic, serologic and roentgen studies must rule out tuberculosis, syphilis, gonorrhea, malignant tumors, and pyogenic infections; (4) changes in bones and joints should be evident roentgenologically. Of their three cases two fulfilled all these requirements. In one case destruction of the intercartilaginous lamina and pubic rami was evident. "In the early phases of the disease arthritic and polyarthritic manifestations may occur, although they are not especially common. Chronic arthritis may occur late in the disease. . . . We report two apparently proved cases of bone necrosis associated with lymphogranuloma venereum and a third case in which such an association is highly probable." Sulfanilamide gave successful results in 15 cases of Nair and Chetty.

Haverhill Fever (Rat Bite Fever). A complete account of Haverhill fever (erythema arthriticum epidemicum) was given by Farrell, Lordi and Vogel. Thirteen reported cases were reviewed and one was added. No attempt was made to resolve the conflict as to the etiologic agent which has variously been described as a *Streptothrix, Haverhillia multiformis* and *Streptobacillus moniliformis.*

[There are presumably two types of rat-bite fever, (1) Sodoku or Japanese rat-bite fever due to a spirochete, the *Spirillum minus,* and (2) that due to the *Streptobacillus moniliformis.*[156, 246] Evidence is accumulating that Haverhill fever is the same as the second type of rat-bite fever. Clinically the two resemble each other closely and the etiologic agent appears to be the same in both. The streptobacillary etiology of rat-bite fever was supported by Dawson and Hobby, who showed that demonstration of the spirillum was only possible by injecting the patient's blood into a susceptible animal. It must be remembered that the spirillum commonly occurs as a harmless saprophyte in experimental animals. Dawson and Hobby concluded that the spirillum theory rested on inadequate evidence.

The relationship between *Streptobacillus moniliformis* and "L forms" or pleuropneumonia-like organisms was discussed at the Third International Congress for

Microbiology in New York (1939). Klieneberger held the view that the "L forms" represented a form of symbiosis but Dienes, Dawson and Hobby were of the opinion that the "L forms" represented a variant phase of the *Streptobacillus moniliformis*. This discussion may assume significance in view of the production of experimental polyarthritis in rats by Collier and Findlay and their associates (discussed under Etiology of rheumatic fever).—Ed.]

Rheumatic Fever

Short general articles on rheumatic fever appeared,[35, 213, 485, 520, 642, 654, 748, 749, 788] also reviews of recent research in the United States [376] and Italy.[614] Keil wrote a historical note on Edward Jenner's lost manuscript on "Rheumatism of the Heart"; the mystery surrounding that important paper remains unsolved.

Incidence. Among 1000 persons under 17 years of age Leslie found 90 who had either a history or physical findings suggestive of "possible rheumatic fever or rheumatic heart disease." But more detailed study of these 90 revealed that only eight had definite, and nine "suspected" rheumatic carditis. Eleven others gave a past history of rheumatic fever (chorea in five instances) but had no residual cardiac damage. Juvenile rheumatic carditis is the commonest single cause of persistently irregular school attendance in London.[35] It accounted for 26.7 per cent of all children out of school three months or longer in 1936. The Public Health Department of London listed as rheumatic 22,800 children under 15 years of age or 2.6 per cent of the total child population of 878,000. But apparently the disease in London is now less severe, since the incidence of rheumatic carditis reported by school physicians decreased from 2.0 per cent in 1926 to 0.77 per cent in 1937, and Glover reported a fall in the crude annual death rate from rheumatic fever and its sequelae in England from 67 per 1,000,000 persons in 1901 to 22 in 1937. The incidence of rheumatic fever is decreasing in the United States also.[748]

In the United States there are probably 1,000,000 persons with rheumatic carditis, according to Hedley; the disease causes 40,000 deaths annually.[373] The incidence of rheumatic carditis among public school and college students is 0.5 to 1.0 per cent; data on the incidence of rheumatic fever among sick children were given for three states (Hedley). Pounders and Gray found 122 cases of rheumatism among 3601 pediatric admissions to hospitals in Oklahoma, an incidence of 3.4 per cent. In Oregon, Bilderback and Overstreet noted rheumatic fever and chorea in 3.45 per cent of 4197 medical hospital admissions. Thompson [764] found a clinical incidence of rheumatic fever of 3.0 per cent among the pediatric patients and rheumatic lesions in 4.27 per cent of the patients coming to necropsy at the University Hospital, Omaha, Nebraska. (Comparable figures indicate an incidence of 4.67 per cent at the Peter Bent Brigham Hospital, Boston and of 0.23 per cent at the Charity Hospital, New Orleans.)

The incidence in Ceylon was given (Fernando): clinical evidences of rheumatic fever were noted in 2.2 per cent of hospital admissions; pathologic evidence was found in 41 (3.6 per cent) of 1110 necropsies.

Predisposing Factors Governing Incidence. 1. Geography and climate. Rheumatic fever is "a very frequent disease in Northern Italy, especially in regions with a continental climate," [614] and in Vancouver "a comparatively mild disease." [39] The disease in Ceylon resembles that in temperate climates.[271] The disease is the same in arctic Russia as in Leningrad.[329]

Studies on dampness and various meteorologic influences threw little

light on the problem. Some [35, 74] found no correlation between cold and damp and rheumatic fever; others [605] considered dampness a factor.

2. Season. The marked seasonal incidence of rheumatic fever was again noted. But differences between seasonal curves for the United States and those for England were not as reported in the past. Thus in Oregon and Oklahoma [74, 605] incidence was highest from December to March and lowest from June to September, while in London it was highest from October to February and lowest from July to September.[35, 321]

3. Social and hygienic factors. The importance of poor housing, inadequate or improper food, and crowding was stressed by Swift and Cohn who noted frequent relapses among children shortly after their return from convalescent homes to their usual home environment. Among one London group of rheumatic children [35] 20 per cent came from "very poor" homes while only 1.4 per cent were from "very good" homes. But the authors noted the danger of drawing conclusions from such an analysis because the population studied was made up chiefly of poor families and did not represent a true cross section. In this study overcrowding was not found to add any "greater risk." According to Glover the disease is 20 to 30 times more frequent among poor children than among rich. The diet of most rheumatic children in London appeared to Jones and Taylor to be adequate.

4. Family, heredity, and constitution. Families of 96 rheumatic children in Baltimore and of 33 nonrheumatic children (controls) were studied by Gauld, Ciocco and Read. A family history of rheumatic fever was obtained 3.7 times as often in the case of rheumatic children as in the controls. "When one or both parents had a history of rheumatic manifestations a greater percentage of the offspring was rheumatic than was found in the offspring of parents who gave no history of rheumatic disease." The percentage of rheumatic female offspring of rheumatic mothers was twice as high as that of rheumatic male offspring, and rheumatic fever was more prevalent among maternal than paternal aunts and uncles. Hence hereditary constitution may play a rôle in the predisposition to rheumatic fever. Sundell described two constitutional types of children predisposed to rheumatic fever. [No data supported this contention which is doubted by many.—Ed.] Hedley noted that the disease is less frequent but more fatal among negroes than white people.

5. Sex. Among 8,000 rheumatic children in London [35] the ratio of boys to girls was 3:4.2 but girls tended to have milder disease. Thus, among 4774 admissions to special juvenile rheumatism units, 40.2 per cent of the boys and 37.4 per cent of the girls gave evidence of cardiac involvement while among 1152 children at the time of dismissal from such units the figures were 38 per cent and 33.3 per cent respectively. In a group of 122 children [605] the ratio of boys to girls was 4.3:5.7, while in another group of 116, boys predominated (57 per cent) except for chorea which occurred 19 times among the girls and 14 times among the boys.

6. Age. The highest incidence of initial attacks occurred at the age

periods of 6, and 11 to 13 years.[74, 605] Bach and his co-authors considered the dangerous period, that from 5 to 12 years; rheumatic fever is "exceedingly rare" in children under 3 years of age; after the age of 11 years it diminishes "until at 14 the risk is one-half that at 5."

Symptoms and Clinical Manifestations of Rheumatic Fever

General Comment. Among 1068 rheumatic children studied by Gibson[312] 459 had had chorea, 650 polyarthritis and 627 cardiac involvement. Of those with chorea, 208 had had no other rheumatic manifestation, 104 had had polyarthritis also, 176 (38 per cent), cardiac involvement and 24, nodules. Among the 650 children with polyarthritis, 157 had only had arthritis, 164 had chorea, 420 had cardiac involvement and 87 had nodules. Of the 627 with heart disease, all but 97 had had either joint pain or chorea. In another series of 122 patients[605] the incidence of symptoms was as follows: carditis, 83 per cent; arthritis and carditis, 59 per cent; chorea, arthritis and carditis, 20 per cent; carditis only, 10 per cent; arthritis only, 9 per cent; chorea and carditis, 9 per cent; chorea only, 6 per cent, and subcutaneous nodules, 4 per cent. [A low incidence of nodules.—Ed.] In London "all clinicians agree that the type of case characterized by acutely swollen joints, sour sweats and severe prostration is now rarely seen."

[One could not make so broad a statement as that in New York City.—Ed.]

Cardiovascular Symptoms. The importance of distinguishing between carditis and inactive rheumatic heart disease was stressed.[78, 436, 748, 754] A classification of the degree of activity of infection based on the percentage abnormality of leukocyte counts was devised.[436] Taussig stated that in children with inactive rheumatic valvular disease further cardiac enlargement does not occur once the heart is adjusted to new conditions imposed by valvular inefficiency; but it does occur when active carditis recurs. The importance of myocardial damage as a cause of cardiac failure in rheumatic carditis has been overemphasized; valvular damage is the important factor (Massie and Levine).

[These authors apparently fail to realize that the most important factor in rheumatic heart disease is that of infection. Doubtless the chief cause of cardiac failure in active carditis is myocardial weakness. What the relative importance of myocardial and valvular damage is in inactive rheumatic heart disease is not so clear. —Ed.]

Parker and Willius noted the difficulty of determining whether massive cardiac enlargement in some cases is due to pericardial effusion or to myocardial dilatation. An analysis of patients with mitral stenosis was made.[229]

Electrocardiographic studies were made in cases of inactive rheumatic heart disease.[18, 229, 518, 629] In 48 per cent of 100 cases studied by Ritchie the auriculoventricular conduction time was greater than 0.19 second, or bundle-branch block or partial auriculoventricular block was present. [In the remaining 52 per cent electrocardiograms were normal in 20, undescribed in 32.—Ed.] Chest leads were used in 10 cases and in two revealed T-wave abnormalities not seen in standard leads. "Rheumatic cardiac patients with persistently prolonged P–R interval are much more likely to develop auricular fibrillation than those whose P–R interval is normal."[18]

Various roentgenologic aspects of rheumatic carditis were presented.[477, 586, 713, 754] Several authors considered anoxemia a cause of myocardial weakness in rheumatic

carditis.[604, 629, 748] Poulton, questioning whether toxins play any part in this, stated that the electrocardiographic changes of carditis can be caused by lack of oxygen and reported differences in the lactic acid content of blood and urine of rheumatic subjects and controls which, he thought, indicated anoxemia.

[No figures were given; the evidence was not convincing. But doubtless anoxemia does contribute to the myocardial weakness in carditis.—Ed.]

The arm to tongue circulation rate in pregnant women with well-compensated rheumatic heart disease is normal but is prolonged when cardiac insufficiency occurs.[157]

Arthritis. Formerly it was taught that growing pains indicate rheumatic fever, but this is not often the case. The differentiation between those of rheumatic and nonrheumatic origin was given.[372, 681, 754, 812] Nonrheumatic pains of children tend to come at the day's end, are in muscles of legs and thighs rather than in joints, seldom involve upper extremities, and are not associated with other signs of rheumatic activity or with abnormal sedimentation rate, leukocyte count or hemoglobin. [They usually represent muscle fatigue from overactivity.—Ed.] The subsequent incidence of carditis in children with nonrheumatic "growing pains" is no greater than that in the general juvenile population.[372]

Subcutaneous Nodules. The incidence of subcutaneous nodules in rheumatic children was 1.0 per cent and 4.0 per cent respectively in two American reports.[241, 605] Fernando found no nodules among 214 rheumatic patients in Ceylon (only nine of his patients were under 10 years of age).

Chorea and Other Neuropsychiatric Manifestations. Schlesinger reviewed briefly the subject of chorea. Of Bauer's [51] 70 choreic patients, 51 had cardiac damage from previous rheumatic episodes or sustained during the chorea. Every one of the 70 had "undoubted rapid sedimentation rates upon admission" and Bauer stated that "careful study will reclassify supposed choreics with normal sedimentation rates in other disease groups." This is contrary to the experience of others,[31, 35, 252] that sedimentation rates are normal in choreics without other rheumatic symptoms.

Ten of Ritchie's 179 rheumatic patients had delirium. One developed cerebral edema with terminal epileptiform attacks. Another had severe headache and rigidity of neck but necropsy revealed no evidence of meningitis. [See section on "pathology of rheumatic fever."—Ed.] Organic lesions of the brain caused by rheumatic fever can induce such varied psychiatric syndromes as dementia praecox, manic-depressive or involutional and senile psychoses, psychosis with cerebral arteriosclerosis and mental deficiency.[111, 112]

[Probably most investigators in the fields of psychiatry and rheumatic fever will be cautious in accepting this last contention.—Ed.]

Neuropsychiatric disturbances appeared in 21 of 23 cases of rheumatic endocarditis studied by Kernohan, Woltman and Barnes: hemiplegia occurred in 10 cases, headache in seven, convulsions in five and chorea in three. There also were instances of twitching of isolated muscles, athetotic dyskinesia, vertigo, syncope, vomiting, fatigue and general weakness. Five patients had psychosis but its relation to the endocarditis of one was not established. Other less severe reactions included delirium, irritability, increased psychomotor activity, emotional instability, insomnia, depression, neurotic behavior and apathy.

[That this was an atypical rheumatic group is indicated by the extraordinary occurrence of hemiplegia 10 times among 23 patients. It also should be noted that the symptoms dis-

cussed by these authors are those of endocarditis and probably not of rheumatic fever per se. —Ed.]

The underlying emotional and psychiatric patterns which tend to govern the formation and expression of symptoms in rheumatic persons were analyzed (Dunbar).

Rheumatic Pneumonia. Nine of Ritchie's 179 patients had signs of so-called rheumatic pneumonia. But Ritchie appeared to question the existence of this disease. Pleurisy occurred in eight cases.

Abdominal Pain. Digilio and Pescatore [6, 230] continued their studies of pain in the left upper abdominal quadrant on locomotion in cases of rheumatic heart disease. The abdominal pain which is a common manifestation of rheumatic fever among children was described by Taussig: "Usually it is not associated with nausea, vomiting, diarrhea, or constipation, but it may simulate acute appendicitis or peritonitis." In two of 116 rheumatic children, abdominal pain led to error in diagnosis and operation for appendicitis.[74] Melena was a striking symptom in a case of rheumatic fever in India.[222]

Excessive Fever. This serious manifestation is seldom reported today: it occurred in four of Ritchie's 179 cases; temperatures reached 108 to 109° F. All four cases ended fatally.

Laboratory Data in Rheumatic Fever

Secondary anemia, often severe, develops during active rheumatic fever but disappears as the infection subsides.[411] Thus anemia may indicate continued rheumatic activity.

Results of studies of glucose tolerance, catalytic potency of blood, and amounts of glutathione in erythrocytes in cases of rheumatic fever and in controls were not constant and disclosed no relationship of rheumatic fever to hyperinsulinism, scurvy or other metabolic anomalies.[661, 662, 666]

The formol-gel reaction was compared with the sedimentation rate of erythrocytes as an index of rheumatic activity.[338, 665] In general the results tended to parallel each other but Schultz and Rose stated that the former differed from the sedimentation rate in that it was positive in rheumatic fever only in the presence of carditis.

[This needs further study; if it is confirmed, the formol-gel reactions would afford important information as to the presence or absence of carditis in rheumatic patients.—Ed.]

Differential Diagnosis of Rheumatic Fever

Several papers on the diagnosis of rheumatic fever appeared.[89, 503, 750, 754, 822] One of the most useful diagnostic measures is the therapeutic test, the response of patients to adequate doses of salicylates.[754] The differentiation between so-called growing pains and mild rheumatic polyarthritis was already mentioned. The significance of the less striking cardiac physical signs was discussed.[754] Synge emphasized the importance of considering

systolic murmurs significant only when accompanied by a definite history of rheumatic fever, cardiac enlargement or diastolic murmurs. Shafar noted the difference between chorea and athetosis of childhood: choreic movements are irregular, jerky, unsustained, and, most important, are not such as might be performed by a normal child; athetosis consists of slow, sinuous, rhythmical movements which blend with one another. The differentiation of juvenile gonococcal arthritis from rheumatic polyarthritis is sometimes difficult.[79] A specific test for rheumatic fever is badly needed.[748] In the absence of such, the sedimentation rate of erythrocytes is the most delicate nonspecific index of rheumatic activity.[39, 252, 363, 754] The formol-gel reaction may also be useful.[338, 665]

Pathology of Rheumatic Fever

General Comment. There has been so much debate as to what should be called an "Aschoff body" that a paper by Aschoff himself defining these lesions is especially valuable; under this term Aschoff includes not only the myocardial nodule but also similar lesions in other organs, e.g., the subcutaneous nodule. He reiterated his belief, also shared by Collins,[177] that the initial tissue change involves the cells; he argued against Klinge's view that fibrinoid degeneration of ground substance is the earliest stage and that cellular changes are secondary. According to Aschoff, myocardial nodules are specific for rheumatic fever.

Heart. Myocardial changes were grouped thus by Ritchie: (1) nonspecific exudative, degenerative and infiltrative processes; (2) abnormalities of mesenchymal cells leading to Aschoff bodies; (3) vascular lesions; and (4) lesions of myocardial fibers. He attributed heart failure not to Aschoff bodies but to nonspecific muscle changes from the "rheumatic toxin" and ischemia. Swift and Cohn likewise stressed the rôle played by rheumatic changes in coronary arteries in causing myocardial weakness. Necropsy in Fernando's 41 cases of rheumatic cardiac disease revealed the coexistence of congenital lesions in three. The incidence of involvement of cardiac valves in Gibson's[812] 73 cases at necropsy was as follows: mitral, 72 cases, aortic, 46, tricuspid, 41 and pulmonic, 8. Pericarditis was present in 62. Reported was the case of a woman, aged 50 years, who died from severe rheumatic pericarditis and myocardial involvement but had grossly normal valves.[145]

Blood Vessels. Italian studies on pathologic changes in large veins and arteries were cited.[614] Lesions in all coats of arteries were noted by Collins.[177] Amorphous fibrinoid material may be deposited in the intima, and later replaced by fibrinous tissue; degeneration may occur in the media, proliferation of connective tissue cells may take place in the adventitia and all coats may be infiltrated with polymorphonuclears, eosinophiles, lymphocytes or plasma cells.

Joints. Studies of synovial tissue[177, 276] revealed edema, fibrinoid degeneration, proliferation of capillary endothelial cells, slight leukocytic infiltration and foci of proliferated mesenchymal cells. Some of the last were multinucleated, making the lesions resemble Aschoff bodies.

Subcutaneous Nodules. The subcutaneous nodules of rheumatic fever are pathologically similar to myocardial granulomas.[27, 629] Hart was unable to repeat the observations of Massell, Mote and Jones (1937) who induced the formation of subcutaneous nodules by injecting blood from rheumatic patients into tissues about their own elbows. Hart obtained completely

negative results from 40 rheumatic and eight nonrheumatic children, also from 10 patients with atrophic arthritis and four with Still's disease.

Brain. In one of Ritchie's cases headache and stiff neck developed. At necropsy multiple small (1 to 2 mm.) foci of ischemic degeneration and scattered arterioles plugged with embolic thrombi were found in frontal and parietal lobes bilaterally, but no evidence of meningitis. Another patient who had epileptiform seizures before death, was found to have cerebral edema at necropsy. Kernohan, Woltman and Barnes reviewed the literature on lesions of the nervous system in cases of endocarditis; small embolic cortical lesions were found in 25 of their 26 cases of rheumatic endocarditis. The cardiac disease was considered healed in most instances; thus the embolic lesions were not part of the pathologic picture of rheumatic fever. In bacterial endocarditis the cerebral lesions were larger and more prominent. In brains of rheumatic inmates of a mental hospital Breutsch and Bahr [111, 112] found obliterating rheumatic endarteritis of small and larger vessels resulting in gross and microscopic infarctions.

Lungs. To Ravenna rheumatic pneumonia was a distinct manifestation with pathologic findings "different from that of any other known disease"; Ritchie doubted the existence of such an entity. Among 179 rheumatic patients were nine who had signs similar to those of "rheumatic pneumonia"; the lungs in two cases which came to necropsy revealed only congestion.

Miscellaneous. Italian work on rheumatic changes in lymph nodes was noted. In Italy some investigators recognize "rheumatic nephritis." [614] Ritchie had one patient, with foci of necrosis to a depth of 2 mm. in the renal cortex.

Relationship of Rheumatic Fever to Other Diseases

To Atrophic Arthritis. Some physicians regard atrophic arthritis as closely related to rheumatic fever, if not one of its manifestations. Fisher [276] considered morphologic changes in joints similar in both diseases, and Kersley described [not very clearly—Ed.] a type of subacute rheumatic infection which tended to "progress to a condition indistinguishable from rheumatoid arthritis." Studies on virus as a possible cause of the two diseases suggested a relationship.[239, 240, 241] Suspensions of virus-like bodies found in rheumatic exudates were agglutinated equally well by serum from cases of rheumatic fever, of atrophic arthritis, or of other arthropathies. Hence Eagles himself has doubted the significance of these reactions. The histologic changes in subcutaneous nodules in rheumatic fever resemble somewhat (but not fully) those in atrophic arthritis, but this does not prove that the two diseases are the same.[177] Italian workers consider the two diseases distinct.[614]

To Exophthalmic Goiter. Rheumatic fever and exophthalmic goiter not infrequently affect the same patient; two such cases were noted by Schultz. Perhaps some underlying constitutional anomaly contributes to the development of both the diseases. Hyperthyroidism may provoke rheumatic activity.[229]

To Dermatomyositis. A case of mitral stenosis with dermatomyositis was seen by Kellogg and Cunha; the relationship was probably coincidental.

Course, Prognosis and End Results of Rheumatic Fever

The prognosis of rheumatic fever must always be considered from the standpoint of the ultimate result as well as that of the immediate attack. Signs and symptoms having a grave immediate import include rapid development of aortic insufficiency, presence of marked cardiac arrhythmia, severe dyspnea and true orthopnea with or without pericarditis, development of marked cardiac enlargement during the attack,[754] excessive fever, the development of congestive failure, persistence of pyrexia for several weeks, tachycardia persisting after fever has ceased and involvement of the aortic as well as of the mitral valve.[629]

[If the author meant that the last four suggest the probable development of serious cardiac damage, we agree, but if he meant that these indicate the likelihood of death during the immediate attack, we cannot agree.—Ed.]

Ritchie considered pleurisy a serious rheumatic manifestation, and stated, "The prognosis in these cases is almost invariably grave."

[We take exception to this view; in our experience rheumatic patients with pleurisy have done as well as the average patient.—Ed.]

The data of Massie and Levine indicate that the immediate prognosis is serious in cases of rheumatic fever and pericarditis. The immediate mortality was 16.3 per cent in their 135 cases; but for the patients who survived the immediate attack, the ultimate prognosis was comparatively good, for 36 per cent of 82 patients given follow-up examinations had no evidence of organic heart disease and an additional 14 per cent had only mitral insufficiency.

An excellent follow-up study was made on 1000 rheumatic children seen by Bland and Jones from 1921 to 1936: by 1936, 239 patients were dead, 744 were living and 17 could not be traced. Of the 744 living, 605 (81 per cent) had no limitation of physical activity (312 had no clinical evidence of cardiac damage), 118 (16 per cent) had slight to moderate limitation and 21 (3 per cent) great limitation of cardiac reserve. Forty-eight per cent of those dead died within four years and 68 per cent within six years. These authors found relatively little difference in prognosis regardless of whether the disease began before five years of age, or between six and 21 years. But others [35, 485] stated that the earlier the age of onset the worse was the prognosis. Of serious prognostic import was the development of marked cardiac enlargement during the initial attack of rheumatic fever.[77] The severity of individual recurrences was of greater prognostic significance than the number of recurrences. In every fatal case of congestive failure, pathologic evidence of active carditis was found even though clinical evidence was sometimes lacking. Taussig also emphasized the rôle played by recurrent activity of the rheumatic infection in congestive cardiac failure of rheumatic children and in the terminal episode. In general, regardless of the patient's age, the chance of a recurrent rheumatic attack subsequent to a respiratory infection decreases the longer the inactive phase of the disease lasts.[429] Of 314 rheumatic children studied by Bland and Jones 25 per cent later presented signs of permanent valvular deformity not present at the time of dismissal from hospital; among two-thirds of these the development of these signs was associated clearly with recurrent rheumatic attacks, and even among the other third indirect evidence suggested that recurrent rheumatic activity had been the cause of the subsequent cardiac damage.

In Russia the younger the child is at his first rheumatic attack, the more frequent the recurrences are likely to be, according to Gornitskaya who found no direct relation between the severity of the first attack and the eventual cardiac damage,

but noted that children who had more than four attacks always were greatly incapacitated. Twelve per cent of his juvenile patients later had normal, 25 per cent considerably reduced, and another 33 per cent markedly reduced functional capacity. Among Gibson's [312] 1068 rheumatic children who were watched for a number of years, 60 per cent sustained cardiac damage. Polyarthritis occurs more often with carditis than does chorea.[312, 329] The longer the interval between the causal attack of rheumatic fever and the appearance of obvious mitral stenosis the better the prognosis.[750]

Mortality rates from heart disease in the United States were published (Hedley). Reports of the ultimate prognosis in rheumatic fever based on studies of patients with carditis must be interpreted with caution since they often do not take into account the rheumatic patients who escape cardiac damage. Thus they give information on the prognosis of *rheumatic heart disease* but make that of *rheumatic fever* appear more grave than it actually is.[748]

Etiology and Pathogenesis of Rheumatic Fever

Factor of Infection. It is agreed that infections, especially of the upper part of the respiratory tract, commonly initiate rheumatic attacks, but it is not agreed that such infections are "specific" provocatives.

Of Ritchie's 100 cases attacks were provoked by such infections in 48, by suppurative appendicitis in two. Among the 749 patients of Jones and Mote respiratory infections (especially sore throats) preceded 58 per cent of the first attacks of rheumatic fever. But the initial rheumatic attack of 37 per cent of the patients began "spontaneously," although in most instances serologic evidence of hemolytic streptococcal infection was found. Approximately half of their patients with inactive disease who acquired "colds" also acquired recurrent rheumatic fever. Of 271 rheumatic exacerbations 67 per cent were associated clinically with respiratory infections, 29 per cent were apparently spontaneous and 4 per cent (12 cases) were associated with trauma or with infections outside the respiratory tract. In another series [35] the onset of rheumatic fever apparently was spontaneous in 621 cases, and followed a "chill" (probably tonsillitis), in only 47 instances. Accidents were considered responsible in one case and fright in three.

Rôle of Hemolytic Streptococci. These bacteria are considered the commonest provocative of the disease.[735] The prophylactic effect of sulfanilamide seems to support the idea that streptococci cause rheumatic fever.[163, 761] Studying the significance of prolonged streptococcal antibody formation in rheumatic fever Coburn and Pauli concluded that it indicates continued subclinical activity of hemolytic streptococci. They also reported [165] a precipitin reaction which occurred when serum of patients, withdrawn during the "silent period" after hemolytic streptococcal infection of the throat, was mixed with serum of the same patients obtained a few weeks later after the onset of rheumatic fever. The nature of the reaction was discussed but no definite conclusions as to its significance could be reached.

In eight of nine fatal cases of rheumatic fever hemolytic streptococci were isolated by Green [336] from gross lesions on cardiac valves but not from heart blood; in the ninth case *Streptococcus viridans* was obtained. In five cases from the throat during life were isolated hemolytic streptococci serologically identical with those isolated from cardiac lesions after death. Among 22 nonrheumatic controls, hemolytic streptococci were cultured from valves only twice and in these cases heart blood also

was positive. Green again[6] discussed[337] the relation of throat infections to rheumatic fever. Antistreptolysin titers were above 100 units in 131 cases of rheumatic fever and below 100 units in 46 control cases. In a histologic study of cardiac valves from rheumatic patients Green found reddish purple, coccoid bodies in gram-stained preparations; whether these were cocci or granules of some sort was not certain, but similar bodies were found in tissues of animals injected with hemolytic streptococci. The results of Green's bacteriologic study of cardiac valves led Collis to report old unpublished results about which he had been dubious: at necropsy in 17 fatal cases of rheumatic fever, hemolytic streptococci were grown from the center of 14 of 15 tonsils, from 13 of 27 cervical or mediastinal lymph nodes, and from 22 of 42 heart valves.

[The work of Green and Collis, if confirmed, will give important support to the hemolytic streptococcus theory. But confirmation is needed.—Ed.]

Other writers[276] doubted that streptococci are related to rheumatic fever (or to atrophic arthritis) because the polymorphonuclear reactions usually found in joint tissues in cases of septic arthritis due to hemolytic streptococci are not found in joints of patients with these diseases. Collins[177] considered the histologic findings in rheumatic joints unlike those of any hitherto proved streptococcal disease but thought that this does not exclude the possibility of streptococcal etiology. According to Ravenna "no Italian believes" in a selective affinity of streptococci for joints and heart. Ravenna described experiments in which chronic foci infected with streptococci were produced in rabbits, following which homologous microörganisms were injected intravenously. Focal myocardial lesions were induced but these were found also in hearts of animals receiving injections of various nonbacterial materials and, to a lesser extent, even in normal controls.

Factor of Bacterial Allergy. This theory has been rejected in Italy.[614] Green[337] noted "miniature rheumatic attacks," which he considered allergic phenomena, following subcutaneous injections of hemolytic streptococcal endotoxin. He was "prepared to admit that certain manifestations of rheumatism such as the flitting joint pains may be attributed to allergy," but he could not believe that allergy alone can account for gross changes in tissue. Collins[177] expressed a similar view. But Levinthal staunchly believed in an anaphylactic (not an allergic) mechanism underlying not only rheumatic fever but also various forms of arthritis and gout. [The theoretical reasoning in this paper was ingenious but the data were presented without convincing evidence.—Ed.] Patients with rheumatic carditis were said by Traut and Vrtiak to have asthma, hay fever and urticaria much oftener than normal controls. Pagel also supported the allergic theory.

The cutaneous reactivity of patients with rheumatic fever or Bright's disease, and of controls, to hemolytic streptococcal nucleoprotein, tuberculin and rabbit serum was studied (Schultz).[664] There were more positive skin reactions to hemolytic streptococcal nucleoprotein among the controls than among the rheumatic patients except for those who had had recent "focal infections." As shown by the development of secondary reactions to rabbit serum, "increased allergic irritability" occurred more often in cases of rheumatic fever or Bright's disease than in control cases. The incidence of this increased allergic irritability was greater among individuals who had suffered recently from focal infections. According to Schultz this is further evi-

dence that alterations in tissue reactivity are associated with rheumatic fever and nephritis.

Virus Theory. Further observations on the agglutination of suspensions of virus-like particles from pericardial and pleural exudates from cases of active rheumatic fever were made by Eagles and Bradley, and Eagles.

The suspensions were tested against serum from 18 patients with rheumatic fever, from 20 with atrophic arthritis and from 16 with other arthropathies as controls. Positive agglutination was obtained in about equal percentages in the three groups (40 per cent, 35 per cent and 42 per cent respectively). There was no consistent relation of agglutination to the clinical stage of disease, and no evidence that it ran parallel to antistreptolysin titers, sedimentation rates of erythrocytes or pyrexia. Attempts to induce disease in monkeys by injecting the suspensions were unsuccessful. Eagles and Bradley questioned whether the so-called virus bodies in rheumatic exudates are true elementary bodies (as in known virus diseases) or are nonspecific bodies that originate in tissue and blood elements arising under abnormal physical conditions of which rheumatic fever is a striking example.

[At the Third International Congress for Microbiology held in New York in September, 1939, Eagles doubted the etiologic significance of these virus-like bodies.—Ed.]

Earlier Italian work on viruses in relation to rheumatism was reviewed by Ravenna who summarized the work of Andrei and himself. They injected whole blood from rheumatic patients into rabbits which were killed three to four weeks later. In 40 per cent they found a widespread endocarditis very similar to that of rheumatic fever, but no myocarditis. But blood from nonrheumatic patients and even milk and horse serum would do the same; perhaps the injected material activated a latent virus in the test animals; in rheumatic fever a virus may be active but only in symbiotic association with streptococci.

" Pleuropneumonia-like microörganisms " were apparently recovered by Swift and Brown from the articular exudate of a patient with rheumatic fever, and from chorio-allantoic membranes inoculated with rheumatic exudates and from " pneumonic lungs " of similarly inoculated mice.

[But at the Third International Congress for Microbiology, Swift and Brown stated that what they originally thought were pleuropneumonia-like microörganisms from rheumatic exudates were either artefacts or microörganisms recovered from the inoculated mice and not related to rheumatic fever.—Ed.]

Vitamin Deficiency. No support was given to the theory of vitamin deficiency.

Factor of Trauma. Trauma plays a secondary, but important, rôle. In needleworkers and laundresses joints of hands and arms tend to be involved early; valvular lesions and subcutaneous nodules tend to develop at sites subjected to local trauma.[748]

Treatment of Rheumatic Fever

Rest. This is the all important remedy in active rheumatic fever.[35, 252, 363, 440, 740, 748, 750, 754] Complete rest in bed is essential in the presence of persisting infection. Sundell favored a cautious trial of sitting up despite occasional slight fever if all other signs are favorable. When the patient is allowed out of bed, the resumption of normal physical activity must proceed

slowly; first gradually increased time in a chair, then cautiously increased walking on the level, finally climbing of stairs and other activity. Convalescent care is important.[35, 440, 748] Needed are more institutions for the sanatorium care of rheumatic convalescents.[364, 748] Although rest is vital in cases of active rheumatic fever, it is not indicated for those of inactive rheumatic heart disease unless definite cardiac decompensation is present.[252, 702, 750] The important factor in inactive rheumatic disease is not rest but the avoidance of a recurrence of the active infection. There is danger of inducing cardiac neurosis by enforcing unnecessary rest on patients with inactive rheumatic heart disease simply because of the presence of murmurs.[702]

Drugs. 1. Salicylates. The effect of salicylates, aminopyrine and other "antirheumatic" drugs on the symptoms of rheumatic fever is great, but these drugs have no effect on the heart.[503, 629, 740, 750, 822] Taussig recommended the auxiliary use of alkali if over 30 grains of salicylates are given in 24 hours. Magnesium carbonate or oxide was the alkali of her choice because of its synergistic action with salicylates in relieving pain. According to her, salicylates relieve precordial and abdominal pain in rheumatic fever.

[These drugs seem to relieve some abdominal pains but not others, depending on their underlying pathologic basis, i.e., exudative inflammation, subperitoneal hemorrhage, arteritis, etc.—Ed.]

Aminopyrine has six times the potency of salicylates as an antirheumatic drug but must be used with caution because of the danger of agranulocytosis.[754]

2. Digitalis. Although the great value of digitalis in relieving congestive cardiac failure and auricular fibrillation in inactive rheumatic heart disease was recognized, some [252, 750, 754] considered its use dangerous in the presence of active carditis.

[To avoid toxic effects digitalis should be given cautiously in cases of rheumatic carditis with prolonged P–R interval, but it is unjustifiable to withhold it, in the face of congestive heart failure and auricular fibrillation, just because the patient has rheumatic activity.—Ed.]

3. Sulfanilamide. Two papers confirmed previous reports that sulfanilamide is not beneficial but may be actually harmful in the treatment of active rheumatic fever [163, 629] or when given in the "silent period" after the onset of a precipitating sore throat.[163] The prophylactic value of this drug is discussed later.

4. Other Drugs. Arsenic for Sydenham's chorea was considered useful by some [613, 655] but not by others.[252] [We agree with the latter.—Ed.] Quinidine can be used for children according to the same principles governing its use for adults.[345] Elghammer was "astonished over the good results sometimes obtained from the use of glucose intravenously during the period of decompensation of the heart."

Removal of Infected Foci. Some writers [252, 750] considered tonsillectomy dangerous during a rheumatic attack and stated that if it is to be done, all signs of rheumatic activity should be gone. Rheumatic children have more marked changes in sedimentation rates and more loss of weight following

tonsillectomy than do nonrheumatic children.[31] But infected tonsils should be removed.[503] Data of Bach and his co-authors indicated that although tonsillectomy before the onset of rheumatic fever does not decrease its incidence, severe cardiac damage was 8.7 per cent less frequent among children whose tonsils had been removed before the onset than among those not subjected to the operation.

Vaccines: Serums. Nothing was reported thereon.

[This is an index of their ineffectiveness.—Ed.]

Fever Therapy. Of 20 patients with Sydenham's chorea given artificial fever by Elkins and Krusen eight obtained complete clinical remissions; seven others, slight to marked improvement. Having treated 70 choreic patients, E. L. Bauer concluded that artificial fever therapy not only stops the choreic attack but also lessens the number of recurrences of rheumatic fever and the extent of cardiac damage. Simmons and Dunn treated 31 rheumatic patients: six of the nine patients with joint pain obtained prompt relief, the remaining three less prompt relief. In 15 of 20 cases the sedimentation rate of erythrocytes fell sharply. Fever therapy was considered by some [154, 269] of value not only for chorea but for the carditis also. But other physicians disagreed.[35, 252]

[The use of fever therapy for rheumatic manifestations other than chorea should be considered experimental.—Ed.]

Diet and Vitamins. Some physicians [32, 539] recommended a diet such as would be suited to any febrile disease. Jones and Taylor found that vitamins B (300 international units), C (2000 international units), A (13,000 international units) or D (2370 units), given daily from February to June were not of any curative or preventive value to rheumatic children.

Miscellaneous. The effect of heliotherapy was not marked, but was pleasing to children so treated.[35] "Improvement" was obtained by 17 of Poulton's 26 rheumatic patients treated in an oxygen tent for from one week to 82 days.

Prevention of Rheumatic Fever

Prophylactic Value of Sulfanilamide. Two important papers concerned the use of sulfanilamide in the prevention of hemolytic streptococcal infections of throat and the subsequent attacks of rheumatic fever. To 80 children with inactive or quiescent rheumatic fever Coburn and Moore gave 2 to 3 gm. of the drug daily, in three doses, for four to eight months: 79 escaped hemolytic streptococcal infections and signs of rheumatic activity; only one child had a respiratory infection followed by a vague illness which may have been atypical rheumatic fever. Thomas and France carried out similar studies on 30 juvenile and adult patients. The dosage was 15 to 20 grains (1 to 1.3 gm.) daily for seven months each in the winters of 1936 and 1937. None of the rheumatic patients receiving sulfanilamide had hemolytic streptococcal infections or rheumatic attacks, whereas four of 30 control rheumatic patients, not given the drug, underwent five major attacks

of rheumatic fever during the same period. None of these patients had to discontinue the drug permanently on account of symptoms of toxicity; but some of those treated by Coburn and Moore had to do so.

[The importance of these studies can scarcely be exaggerated if the results are borne out by further work.—Ed.]

Other Measures. A course of salicylates given for one week every month helps prevent rheumatic recurrences according to E. L. Bauer. [Most American workers would not agree, nor do we.—Ed.] The value of certain general measures for preventing rheumatic fever and carditis was stressed,[373] such measures as improved living conditions, prolonged convalescent care, better and earlier case finding by school health officers.

Public Health Aspects. Rheumatic fever is one of the major American public health problems.[373] It should be a reportable disease[748] as it is in Italy.[614] In Philadelphia during 1936 rheumatic heart disease was exceeded only by tuberculosis, lobar pneumonia and syphilis as a cause of death; it caused more deaths of persons under 20 years of age than whooping cough, measles, meningococcal meningitis, diphtheria, scarlet fever and poliomyelitis combined.[373] Rheumatic fever and rheumatic heart disease have been neglected greatly by health authorities; more furore is raised over one case of leprosy than over 100 cases of rheumatic fever. Facilities for the proper care of rheumatic cardiacs are woefully insufficient in the United States.[748] In view of the cost of keeping such patients in general hospitals, the problem could be solved more economically by providing suitable sanatoria where the cost per patient would be lower and problems peculiar to rheumatic fever could be more carefully studied.[748] Plans for the care of rheumatic school children were reported.[364, 440, 668] The rôle of the social worker and psychiatrist is important; the diagnosis should be made early enough in life so that victims can be rehabilitated and taught trades within the probable limits of their future physical capacities.

"Every rebuilding scheme, every slum destroyed, every new hygienic school built, every playing field provided, every increase in the standard of living, every improvement in the knowledge of nutrition, helps to decrease the incidence of acute rheumatism."[322]

The London County Council's Rheumatism Scheme was described.[35] This comprehensive plan for the supervision of rheumatic children under 16 years of age has five general aims: (1) gradual amplification of special rheumatism units until there are enough beds to provide for an average period of treatment of six months for all children with active rheumatic fever; at the time of the report, 650 beds were available for acute and subacute cases, and 250 more for doubtful or very mild cases; these units are recognized by the Board of Education as "hospital schools" and staffed by qualified teachers; (2) establishment of "rheumatism supervisory centers" for early diagnosis and supervision of quiescent cases; 21 were in operation in December, 1938, handling 5160 children; (3) establishment of an alternative system of supervision by school physicians; (4) investigation of the child's home environment by special workers; unsatisfactory conditions are reported to the Borough Medical Officer of Health; (5) central coördination of various branches of the scheme.

In addition to these facilities provided by the London County Council there are in London 467 beds in voluntary children's hospitals and 233 beds in "heart homes" and hospital schools other than those of the Council's units, also out-patient facilities and beds in hospitals not especially for children. The medical supervision, treatment, and special education of rheumatic children costs the city of London about $1,000,000 yearly; despite this about 20 per cent of the children sustain enough cardiac damage to render them unable to be self-supporting after leaving school.[35]

Erythema Nodosum

Erythema nodosum is considered by some a common, by others a rare, accompaniment of rheumatic fever. The view that it is a nonspecific skin reaction which may occur with different infections received support from a study of acute coccidiosis among children by Faber and associates.

Acute coccidiosis is an acute febrile disease caused by the fungus *coccidioides immitis* and is characterized by initial systemic symptoms not unlike influenza. It is often followed by erythema nodosum and accompanied by specific sensitivity to the products of the fungus. The disease has long been known in the San Joaquin Valley, California, but sporadic cases have been noted elsewhere. The mortality rate of coccidioidal granuloma is 50 per cent; the acute form has caused but one death in 700 cases. It is common among children, and in 22 of the 24 cases noted, typical lesions of erythema nodosum were present. In nine of these, acute arthritis was noted also and involved knees and ankles, in one case a shoulder. The joints were tender to pressure and painful on motion but not red. Diagnosis was established by skin testing with 0.1 c.c. of a 1:1000 solution of coccidioidin. No specific therapy is available.

The connection between erythema nodosum and tuberculosis was discussed.[350, 699, 763] Thompson [763] regarded erythema nodosum as a sign that the host had developed resistance (immunity) as well as skin hypersensitivity (allergy).

Erythrocyturia was observed by Wallgren in every third or fourth case of erythema nodosum among 88 children. The phenomenon was considered similar to capillary fragility.

Chronic Arthritis: The Two Common Types

No new statistics on the incidence of the two great types of chronic arthritis (atrophic and hypertrophic) were reported.

Relationships. The orthodox differentiation of these two types was given.[51, 542, 628, 801] It is often said that atrophic and hypertrophic arthritis are expressions, at opposite ends of the same scale, of a single disease. Having studied their comparative pathology Collins [178] emphatically disagreed with this idea. According to him they are totally different diseases even though secondary hypertrophic changes may occur late in the course of atrophic arthritis. It is commonly [but erroneously—Ed.] believed that persons with atrophic arthritis are usually tall and thin, those with hypertrophic arthritis shorter and stout. The mean height of Weber's 64 patients with atrophic arthritis was 68.1 inches, the mean weight 146 pounds;

the mean height of his 21 patients with hypertrophic arthritis was 67.8 inches, the mean weight 162 pounds.

[To him this difference was "impressive"; to us it is not. The average age of the latter group was eight years more than that of the former.—Ed.]

Atrophic (Rheumatoid, Proliferative, Infectious) Arthritis

Influence of Age and Heredity on Incidence. In Monroe's 267 cases the disease began at an average age of 32 years, before the age of 10 years in 3 per cent, after the age of 60 years in 2 per cent. About 20 per cent of his patients gave a history of atrophic arthritis or of rheumatic fever in parents or siblings.

General Clinical Data: Symptoms and Course of Atrophic Arthritis. The disease was, as usual, divided by some writers [51, 207, 410] into two varieties or species: (1) "primary" or "typical" atrophic (or rheumatoid) arthritis, and (2) "active infective," "atypical" or "secondary atrophic" (or rheumatoid) arthritis. [These have been described in previous Reviews.—Ed.] Under the term "subacute rheumatic infection" Kersley described cases of young adults, many of whom had had rheumatic fever, chorea or growing pains, who later had transient articular pains and swellings without notable anemia or increased sedimentation rates; some had "a tendency for slight fusiform swelling of the joints to persist and slight contractures to occur merging into a rheumatoid or periarticular fibrositic syndrome."

[His data were insufficient to clarify the vague term used.—Ed.]

Clinical details in two new series of cases were reported. In 52 per cent of Weber's 64 cases the disease began acutely. The following joints were affected: knees in 64 per cent; ankles in 33 per cent; hips in 32 per cent; spine in 30 per cent; feet in 28 per cent; shoulders in 25 per cent; wrists in 23 per cent; hands in 19 per cent [an unusually low incidence in hands—Ed.]; elbows in 6 per cent; jaws in 2 per cent. Subcutaneous nodules were present near elbows in 3 per cent, on fingers in 6 per cent. Functional cardiac murmurs were present in 22 per cent of cases; organic cardiac lesions were found in none.

Of Monroe's 267 patients whose average age was 39 years and whose "arthritic age" averaged seven years, 30 per cent were overweight (average 32 pounds), 41 per cent were of normal weight, 28 per cent were more than 20 pounds underweight. "Ten to fifty per cent of the original body weight may be lost within a few months." Joints affected were in the fingers in 70 per cent of cases, knees in 54 per cent, ankles in 52 per cent, wrists in 48 per cent, lumbar vertebrae in 35 per cent, elbows in 34 per cent, shoulders in 34 per cent, thoracic vertebrae in 26 per cent, hips in 26 per cent, sacro-iliac joints in 20 per cent, toes in 14 per cent, jaws in 4 per cent, sternoclavicular joints in 0.5 per cent. [Note that in this series hands, wrists and elbows were affected much oftener than in Weber's series, feet less often.—Ed.] In Monroe's cases "valvular heart disease" occurred in only 4 per cent, hypertensive and arteriosclerotic heart disease in only 5 per cent. A clinical chart for chronic arthritis was devised.[354]

Atrophic Arthritis: Special Clinical Features

Effect of Toxic Hepatitis and Jaundice from Cinchophen. Another example of the beneficial effect of toxic hepatitis and jaundice on atrophic arthritis, even though of long standing, was reported.

Lichtman saw a man, aged 47 years, who had had painful knees for 10 years. The pain at night was so severe that he "could not cross his knees in bed and was compelled to assume unusual postures to avoid pain." After taking 15 grains of cinchophen daily for a few days he developed generalized pruritus and later painless jaundice with greenish brown stools. Icterus index was 27 units, serum bilirubin 4.5 mg. per cent, van den Bergh reaction positive. Blood cholesterol was 355 mg. at first, 250 mg. per cent two weeks later. "The patient noted from the very onset of his jaundice that he was completely free of the pains in his knee joints with which he had suffered persistently over a period of ten years." Within six weeks the jaundice disappeared: "with the disappearance of jaundice the joint pains returned."

[Roentgenograms did not reveal any changes in knees after 10 years of illness therein; despite this Lichtman believed that atrophic arthritis was present. A week after the pains returned to the patient's knees stiffness of fingers also developed.—Ed.]

Of interest in this connection is the observation of Boots that patients with atrophic arthritis frequently present redness of the thenar and hypothenar eminences of the hands, similar to the "liver palms" of patients with cirrhotic livers. The finger tips may show this same redness. Perhaps the liver is involved in both of these conditions. This so-called liver palm is also seen sometimes in peripheral vascular disease.

Effect of Urticaria (without Jaundice) Produced by Cinchophen. Under certain conditions actual jaundice is not necessary for the appearance of the phenomenon just mentioned. Complete relief of arthritic symptoms may occur following urticaria from cinchophen toxicity without jaundice.

In 1933 Hench reported a case of atrophic arthritis with complete cessation of pain following urticaria which arose after cinchophen administration but which appeared six weeks before the onset of visible jaundice. Rawls [615] has confirmed this observation. In studying the relation of cutaneous sensitivity, hepatic function, leukopenic index and toxic effects from cinchophen he noted the onset of urticaria from cinchophen toxicity in nine cases. Jaundice occurred in none, but in five cases notable amelioration of arthritic symptoms occurred. With the onset of urticaria in three cases or just after its disappearance in two cases there was marked diminution of articular pain, tenderness, swelling and stiffness: relief was complete in three cases, almost complete in two cases and lasted from five weeks to five months. The relief was proportional to the severity and duration of the urticaria and was "far more striking than that obtained with cinchophen per se."

[Obviously in cinchophen toxicity several different chemical reactions occur: that which relieves articular symptoms is not the one which produces urticaria; also it appears that actual hyperbilirubinemia is not necessary for the relief of joints.—Ed.]

Effect of Pregnancy. During pregnancy joint pains are almost always definitely less "due to the fact that glandular activity is stimulated and resistance to infection is at its best; after childbirth when such stimulation has subsided there is frequent exacerbation of joint symptoms" (Burbank). In contrast to the relief of atrophic arthritis by pregnancy is the pelvic osteoarthropathy that may develop during pregnancy in nonarthritic women (Young).

Ocular Lesions Complicating Atrophic Arthritis. In about 2.5 to 4.5 per cent of cases of atrophic arthritis iritis develops according to Berens, Angevine, Guy and Rothbard. Ocular lesions (iritis, cyclitis, uveitis) which may complicate atrophic arthritis or spondylitis were described by Juler.

Attacks generally last two to six weeks (unless the ciliary body is affected) and often recur. Treatment includes local therapy for eyes, removal of infected foci (even of questionable foci in recurrent cases) and protein shock therapy with milk or typhoid vaccine.

Pathologic Characteristics of Atrophic Arthritis

Synovial Membrane. There are two chief microscopic synovial lesions in atrophic arthritis: (1) regions of fibrinoid degeneration surrounded by a corona of fibroblasts; Fisher[5] considered these lesions similar to those of rheumatic fever and many now regard them as the primary and perhaps the specific tissue change in "rheumatism"; (2) large follicle-like collections of lymphocytes or plasma cells; these are considered specific for atrophic arthritis by some,[6] but not by others. According to Collins[177] neither of these lesions is specific: fibrinoid swelling of collagenous connective tissue appears under certain non-specific stimuli whether or not tissues are hypersensitive; the large foci of round cells probably represent a nonspecific synovial reaction to any chronic inflammation. Collins presented an unpublished microphotograph of W. E. Swift showing similar collections of lymphoid cells in synovial villi of a tendon sheath in a case of chronic traumatic tenosynovitis without evidence of atrophic arthritis or rheumatic fever. [Could the patient have been developing early atrophic arthritis? A follow-up note on this case would be interesting.—Ed.] Late in atrophic arthritis secondary osteo-arthritic changes may occur.[178]

Laboratory Data in Atrophic Arthritis

Roentgenograms. No new data were presented.

Hemoglobin, Cell Count and Hematocrit. A moderate hypochromic anemia was present in many of Monroe's 267 cases: in 25 per cent values of hemoglobin were between 50 and 70 per cent; erythrocyte counts ranged from 3,500,000 to 4,200,000 per cubic millimeter. During acute exacerbations leukocytosis (generally 9,000 to 13,000, rarely over 18,000 cells per cubic millimeter) often occurred. Collins, Gibson, Race and Salt considered hematocrit estimations of packed red cell volume easier to do routinely and more informative than erythrocyte counts. Information concerning erythrocytes (degree of anemia in terms of volume of erythrocytes), leukocytes (depth of leukocyte cream) and plasma (presence of subclinical icterus) can be obtained thereby.

The mean percentage of nonfilamented leukocytes in Stiles' 14 cases was 36.9 (normal 7 per cent or under).

Sedimentation Rates. Yeoman noted changes in sedimentation rates in 40 cases after a course of spa therapy alone or with chrysotherapy, female sex hormones or typhoid vaccine. Improvement in sedimentation rates occurred in most of the patients treated by spa therapy alone. Improvement in rates generally (but not always) paralleled clinical improvement.

Other papers on sedimentation rates discussed the history of the test, comparisons of various methods, and the factors which influence the results.[356, 424, 504, 637] Chief factor regulating erythrocyte sedimentation is fibrinogen according to some, globulin according to others. Ropes, Rossmeisl and Bauer found no absolute correlation between rates and the plasma protein fractions. They concluded that "variations in rates are due to variations in the colloidal state of plasma with consequent changes in the electric charges on the proteins and red cells. Variations in the concentration of fibrinogen, globulin and other constituents affect the rate through their effect on the colloidal state of plasma." Ham and Curtis also noted that the rate may fail to correlate in a linear manner with fibrinogen when the serum globulin is elevated or erythrocytes are notably altered in size.

In view of the effect of pregnancy on atrophic arthritis the following data are of interest. During pregnancy the plasma volume increases and produces hydremia which may be correlated with an increase of globulin.[310] The sedimentation rate increases during pregnancy[424] from the tenth or twelfth week and does not become normal until three or four weeks postpartum (Wintrobe, 1937).

[The period when rates are elevated corresponds closely with that during which the ameliorating effect of pregnancy is usually noted.[6]—Ed.]

Normal values for sedimentation rates in different age groups were established by Osgood and colleagues. No significant sex differences were noted; a sedimentation rate of 15 mm. at the end of 45 minutes (Westergren method) was considered the upper limit of normal. The Westergren method was regarded by many as the simplest and most reliable.[360, 573] Others described "simpler" methods: that of Brooks involved the use of a venipuncture needle on the end of the marked pipette used for the test; this allows the pipette to be filled directly from the vein and then to be set vertically in a holder. Goldberger's "rapid bedside test" involved the use of unspread blood films on slides: characteristics of the cellular meshwork depend directly on the sedimentation rate. More elaborate and presumably more accurate tests were described.[209, 560] Collins, Gibson, Race and Salt favored a wide-bore tube method using oxalated blood and permitting correction of the result to a standard erythrocyte volume. Their method is used in the four largest British hospitals for rheumatic diseases. As an anticoagulant they preferred oxalate to citrate which may retard the rate. But others considered citrated blood more stable; oxalated blood must be tested within the hour.[65, 360, 607] Some workers concluded that the correction of sedimentation rates for anemia gives results which are more often misleading than helpful,[360] but others considered such correction generally necessary.[343]

To avoid one of the complicating factors (fibrinogen) Coke developed his differential serum sedimentation test.[172, 173, 174, 207] It is a modification of Bendien's test for cancer. Characteristic curves were noted for fibrositis, atrophic arthritis, "infective arthritis," osteo-arthritis and "spondylitis adolescens." Coke and Crowe considered this test useful in controlling gold or vaccine therapy to avoid toxic reactions. Gibson[310] considered it useful but not favored in England. According to Shackle much more work is needed to establish the claims made for it: "It is doubtful if it has any affinities with the [erythrocyte] sedimentation rate at all."

Blood Chemistry. Serum proteins in 75 cases of atrophic arthritis (48 "severe," 27 "moderate") were studied by Scull, Bach and Pemberton. Average values for total protein were essentially normal; those for serum albumin were normal or slightly subnormal, those for serum globulin, normal

or somewhat elevated; thereby a reduction was produced in the albumin-globulin ratios. Deviations were not diagnostic.

[The classification of the arthritides used in this paper is confusing and represents quite a departure from that previously used by the same authors. They have included as "rheumatoid diseases" not only atrophic arthritis and spondylitis but also hypertrophic, syphilitic, tuberculous and even gouty arthritis. To add to the confusion, an additional undefined group of "miscellaneous rheumatoids" was included and no definition of the "non-rheumatoid controls" was given. Rheumatologists are trying to establish a precise, universally understood meaning for the (synonymous) terms "atrophic and rheumatoid." The indiscriminate broadening of the meaning of the term "rheumatoid disease" as in this report is regrettable.—Ed.]

In 68 per cent of the 50 cases of Rawls, Weiss and Collins values for serum albumin were subnormal, i.e., less than 4.5 mg. per 100 c.c. of serum (actual figures were not given). There was an abnormal albumin-globulin ratio (under 2) in 38 (76 per cent) of the 50 cases: ratios were 2 to 2.8 in 12 cases: 0.6 to 1.8 in 38 cases. These results with other data supported the idea that hepatic dysfunction often occurs in atrophic arthritis.

Concentrations of serum phosphatase studied by Steinberg and Suter were about normal (average normal 3, upper limit of normal 4.2 Bodansky units) in 44 cases of atrophic arthritis regardless of the degree of involvement, stage of disease or age of the patient, except that prolonged disease tended to lower the phosphatase content. Values ranged from 1.6 to 2.8 (average, 2.3) units. A point of diagnostic significance to be recalled is if a patient with atrophic arthritis presents an elevated value for serum phosphatase, suspect some coincident bone disease, e.g., malignancy or osteitis deformans. [An important point.—Ed.] Values were also normal in hypertrophic arthritis. These results agreed essentially with those of Smith, Klein and Steck. They considered as normal 1.5 to 4 units; in their 18 cases of atrophic arthritis the average value for serum phosphatase was 2.69, lowest 0.44, highest 5.40 units. The daily use of massive doses (150,000 to 400,000 units daily) of vitamin D tended to decrease the serum phosphatase. Similar results before and after such therapy were also seen in cases of hypertrophic arthritis.

Glucose tolerance tests gave normal results (blood sugar 80 to 130 mg.) in all of 11 cases studied by Weber. Liver function tests will be noted under "Etiology and pathogenesis: hepatic dysfunction."

Synovial Fluid. In acute atrophic arthritis the O_2 tension of synovial fluid is higher and the CO_2 tension is lower than normal, perhaps because of some "interference with the blood and/or lymph supply to the joint" (Savage and Taylor). The vital azo dye, T–1824, or Evans blue, when injected intravenously combines with serum proteins to form a large molecular aggregate which cannot pass through uninjured, but does pass through injured, capillary endothelium. Burman and Kling injected it intravenously in five cases of atrophic arthritis; in all cases it appeared in synovial effusions. Measuring the concentration of the dye in synovial fluid may give an index to the activity of synovial inflammation in a given case: the more acute the arthritis, the greater the concentration of the dye in synovial fluid.

[But the sedimentation rate of erythrocytes is a much handier and probably more accurate index of the degree of inflammation.—Ed.]

Basal Metabolic Rates. These will be noted under "Etiology and pathogenesis: factor of endocrine abnormality."

Etiology and Pathogenesis of Atrophic Arthritis

Factor of Infection. No new data of significance were reported to support or refute the infectious theory.

1. Foci. A wide divergence of views regarding the importance of septic foci is held in America and Europe. In the United States opinion is apparently less unanimous than it is in Germany where much importance is attached to such foci.[757] Gingivitis was considered more important than periapical infection by Cogan and demands special dental therapy, not just "cleaning." Monroe, however, considered gingivitis unimportant and root abscesses (present in less than 10 per cent of his cases) "greatly overrated as a source of arthritis." To him infected tonsils seemed more important. Infected teeth and tonsils were present in 75 per cent of Weber's 64 cases. Infected sinuses, including "silent sinusitis," have been considered by some[1, 5] to be commonly present in cases of atrophic arthritis. Hamblen-Thomas noted sinusitis among 18 to 60 per cent of "chronic rheumatic patients" referred to him in different years. [Doubtless the incidence was high because probably only patients with suspected sinusitis were referred to him, a nose and throat specialist.—Ed.] Others (e.g., Anderson, 1930) rarely found sinusitis among arthritics. It was present in 5 per cent of Monroe's cases. Williams and Slocumb found roentgenographic evidence (cloudiness) of sinusitis in 42 of 100 cases of atrophic arthritis, but sinusitis was clinically active in only 20 cases. In one of these 20, roentgenograms did not give evidence of sinusitis.

Infections of prostate, female pelvis, gall-bladder and intestines rarely cause arthritis, according to Monroe, but Fishbaugh frequently incriminated the colon: in 80 of 140 cases of "chronic arthritis" [type unstated—Ed.] articular symptoms waxed and waned with intestinal symptoms. Constipation made the joints worse; "starvation" (undefined) lessened articular pain and swelling. [The temporary relief of articular pains which catharsis sometimes produces may result from the removal of water from the body, according to some workers.—Ed.] Present were fermentation of stools in 118, colonic stasis in 140, diverticulosis in 23 cases. According to Meyer: "Infections in veins, and not in diseased teeth and tonsils, are the most prevalent focal infections and therefore, the most frequent cause of rheumatism." He allegedly found "latent phlebitis" of the legs and "latent jugular phlebitis" in "nearly every rheumatic condition." "Jugular phlebitis is the missing link between oral infection and rheumatism."

[No proof for these statements was given and they are contrary to our experience.—Ed.]

A summary of Rosenow's numerous studies on the relation of streptococci to focal infections and on the characteristic cataphoretic velocity and elective localizing power of these bacteria in cases of chronic atrophic arthritis was reported. By studying the precipitation reactions of the serum of patients and the serum of horses hyperimmunized with the streptococci,

and the erythematous reactions to intradermal injections of euglobulin fraction of antistreptococcal serum, Rosenow obtained what he considered to be serologic proof of the specificity of the streptococci isolated.

2. Blood Cultures. Studies of blood cultures seemed "useless" to Shackle. But Traut who found pleomorphic bacteria in the blood in 71 per cent of his cases of "chronic arthritis" stated his belief that many of the "different" bacteria recovered by various workers may have been mutations of one organism. Dissociation of Traut's organism occurred especially in the blood of patients with chronic, but not with acute, alcoholism. The dissociating factor was independent of the amount of alcohol in the blood. But the blood of guinea-pigs made alcoholic for five weeks did not cause the tested bacteria to dissociate.

3. Joint Cultures. Aerobic cultures of synovial fluid in about 80 cases were "invariably sterile" (Collins). Synovial fluid is highly bactericidal; "Can we be sure that joint *tissues* in the early stages of the disease are always sterile?"

4. Agglutination Tests. For the first time in several years no new studies were reported thereon. They were considered "of doubtful significance" [676] and not of sufficient value to be done routinely.[51]

5. Precipitin Tests. No data thereon were reported except those by Rosenow just noted. In 67 per cent of 12 cases of atrophic arthritis the serum gave positive precipitation reaction to the serum of horses hyperimmunized with "arthrotropic streptococci"; in 50 per cent, to serum of horses immunized with "encephalitis streptococci"; in 0 to 8 per cent, to serum of horses immunized with streptococci from other diseases. Bauer [51] considered streptococcal precipitin tests of little diagnostic value.

6. Antistreptolysins. No new data were reported. Estimations gave titers "too variable for value." [676]

7. Antifibrinolysins. No data were reported.

[Apparently investigators are getting as discouraged in interpreting indirect serologic evidence as they are in evaluating the direct cultural evidence of the infectious nature of this disease.—Ed.]

8. Skin Tests. In 42 cases Rosenow noted that the erythematous reaction to intradermal injections of the euglobulin fraction of various antistreptococcal serums was much larger against the euglobulins prepared with streptococci from cases of arthritis than against those from any other cases. Skin tests with filtrates from various bacteria isolated from different foci were used by Anderson, Lamb, Barrett, and Nerb to determine which filtrates should be used to "desensitize" patients. The commonest organism considered responsible was an alpha (green producing) streptococcus from stools. All of Reeves' [unstated number of] cases of atrophic arthritis demonstrated cutaneous hypersensitivity to streptococcal antigens: in a third the reaction was only to indifferent streptococci, in a third only to *Streptococcus viridans,* and in a third to all of three antigens (from *Streptococcus viridans,* hemolytic, and indifferent streptococci).

9. Complement Fixation Tests. No data were reported.

Theory of Bacterial Allergy. This theory was favored by several.[263, 385, 483, 621] Hicks and Wyatt employed a "specific leukopenic index to streptococci" to uncover evidence of streptococcal allergy and to measure the amount of desensitization accomplished in cases of atrophic arthritis by means of streptococcal vaccines given intravenously.

Vaughn (1934) fed patients test foods on a fasting stomach and noted subsequent variations in leukocyte counts at four half-hour intervals. Ordinary leukocytosis followed the ingestion of food to which the patient was not allergic, but leukopenia followed the ingestion of food to which the patient was known to be highly sensitive. Ishmael (1937) noted that leukopenia similarly follows the intravenous injection of small amounts of a streptococcal substance in cases of atrophic arthritis. Hicks and Wyatt noted that in normal control cases and in cases of hypertrophic arthritis leukocytosis followed the intravenous injections of a streptococcal protein and in cases of atrophic arthritis it followed the intravenous injection of a substance from *Staphylococcus aureus* and *Bacillus typhosus*. But in the cases of atrophic arthritis, when the streptococcal protein was used, leukopenia always resulted. In 34 such cases the leukopenia ranged from 15 to 52 per cent and averaged 31 per cent. Hence the degree of leukopenia produced was used as a gauge of the sensitivity, to streptococci, of a given patient with atrophic arthritis. A course of vaccine given intravenously diminished the average leukopenia by about 50 per cent, i.e., it "diminishes the allergy" by about 50 per cent. These results were considered "major evidence that the essential etiology of atrophic arthritis is a combination of streptococcus focal infection coupled with induced or constitutional hypersensitivity to the protein of this organism. In other words, the host factor is streptococcus allergy."

Discarding the term "allergy" because of its vagueness Levinthal considered that all the rheumatic diseases represent "anaphylactic reactions." Space does not permit an adequate synopsis of his concept; the original reference should be consulted.

[This is an interesting but a hypothetical paper with few data to support the writer's ideas. It should be read in connection with that of Pagel in which the probably allergic nature of rheumatic granuloma and their relationship to the epithelioid cells of tubercles are discussed.—Ed.]

According to Monroe, Traut and Vrtiak patients with atrophic arthritis are no more subject than nonrheumatic persons to the commoner well-recognized allergic diseases, asthma, hay fever and urticaria.

[The conclusion of Traut and Vrtiak seems at variance with their tabulated data which indicated that allergic diseases were less frequently associated with atrophic arthritis than with hypertrophic arthritis or rheumatic heart disease but were still more frequent than among patients used as controls. The percentage incidence of various diseases in 100 cases used as controls and in 175 cases of atrophic arthritis respectively was: asthma 2 and 5.2; hay fever 1 and 12.6; urticaria 13 and 21; eczema 5 and 8; rhinitis 14 and 25; migraine 18 and 36. In other words these diseases were generally about twice (hay fever about 12 times) as frequent among the arthritics as among the controls.—Ed.]

Virus Theory. Eagles discussed further the isolation by himself and his colleagues [5, 6] of virus-like bodies from the exudates of patients with atrophic arthritis (and rheumatic fever), their agglutination by the patients' serums but their failure to produce rheumatic lesions in monkeys.

Dyson found no bacteria in synovial fluid in a case of "multiple arthritis of some duration with deformities," but when the fluid was injected intraperitoneally into a guinea-pig, a delayed fatal pericarditis occurred. Injections of the pericardial fluid into other guinea-pigs also produced a similar reaction. A pneumococcus type 19 was finally recovered but since this organism does not produce such delayed lesions in guinea-pigs, Dyson suggested that a virus was present in the original synovial fluid.

Factor of Trauma. The rôle of chronic postural trauma in the production of chronic atrophic (and hypertrophic) arthritis was discussed.[430]

Factor of Circulatory Disturbance. Sluggish circulation in nail capillaries was found by Dacso in 24 of 32 cases: circulation was normal in eight, slow in 13, decidedly slow in nine and in two entire stasis was seen. Such changes in peripheral circulation, though mild, doubtless influence the production of articular pain and deformity. Using the plethysmograph as a "more accurate method" for measuring circulation in fingers than skin thermometers Ghormley and Silverglade found no consistent vascular reactions or alterations in atrophic arthritis. Circulation was diminished in some cases, increased in others, normal in others. According to Collins[176] some patients with atrophic arthritis under certain conditions present, not an organic obstruction to blood flow, but a reduced flow through smaller vessels. The disorders are of function, not of structure; although blood flow is probably adequate for tissues in a resting state, it is inadequate to permit proper repair of tissues, and is deficient in the presence of physiologic emergencies. Patients with Raynaud's disease react somewhat like those with atrophic arthritis but the two diseases do not produce similar lesions. The vascular disturbances in atrophic arthritis are probably not the cause, but the result of the disease. Apropos thereof Pemberton remarked: "The fact that Raynaud's disease is not accompanied by classical arthritis does not constitute evidence that disturbances in the finer circulation bear no relation to arthritis."

Factor of Altered Metabolism. Attempting to rationalize sulfur therapy in chronic arthritis Wheeldon and Bosher studied the blood and urine in 74 cases of atrophic or hypertrophic arthritis. Results for the two types were not analyzed separately but normal concentrations of glutathione, inorganic sulfates, total sulfur and total sulfates in blood and of urinary sulfates were found. Despite this many patients "improved" on sulfur therapy. The cystine content of nails was high in some of Sullivan's cases of "arthritis," [types not stated], low in others. Since it is low in other diseases the deficiency is not specific or diagnostic. Comroe studied the cystine content of nails in 215 normal persons: the normal variation was greater than previously reported; there was a normal distribution about a median of 9.7 with a quartile dispersion between 8.8 and 10.6. The cystine content of nails was normal in a fair percentage, but low in the majority of 100 cases of atrophic arthritis.

[So far no abnormality of sulfur metabolism in atrophic arthritis has been demonstrated.—Ed.]

Factor of Vitamin Deficiency. The content of vitamin C in serum was subnormal in 75 per cent of the 56 cases of atrophic arthritis of Hall, Darling and Taylor; in 59 per cent it was below 0.5 mg. per 100 ml. (normal 0.8 mg. or higher). Although some patients were taking diets low in vitamin C, none had scurvy. Ten patients tolerated an intake of 100 to 200 mg. without marked excretion in urine; apparently, patients with atrophic arthritis demand much more vitamin C than normal persons. Although patients of Sherwood and Thomson were on diets adequate in vitamin C, their blood was deficient in this vitamin: this was interpreted as indicative of an abnormal vitamin C metabolism rather than a heightened need for it. Similar results were found in cases of hypertrophic arthritis.

[Further studies on vitamin C should be made. Until we have methods for studying the intermediate metabolism of vitamin C the abnormalities observed cannot be interpreted.—Ed.]

Food Allergy. Some patients state that certain foods aggravate their arthritis, but the factor of food allergy in this disease remains unproved. "The matter really appears to be one of fear and distaste, for proof of sensitivity is lacking on skin tests and elimination diets. I have not seen a case" (Monroe).

Intestinal Toxicosis. The supposed rôle of constipation, intestinal toxicosis and colonic irregularities was discussed in the usual vague manner. Some dyspeptic symptoms are the result, not the cause, of the disease.[275, 325, 415]

Hepatic Dysfunction. There is a growing belief among some workers that the liver plays a rôle in the production of atrophic arthritis. Whether this is a pure metabolic dysfunction or is due to failure of the liver in the work of detoxication is not clear. Chief difficulty is to devise a liver function test delicate or specific enough for use in mild cases.[182, 187, 539]

Rawls, Weiss and Collins continued their studies of hepatic function in atrophic arthritis. Several tests were used. The azorubin S test revealed hepatic dysfunction (delayed excretion, too rapid excretion, or reduced ability to concentrate the dye) in 60 per cent of 50 cases. Excretion of hippuric acid was abnormal in 62 per cent; it was below normal in 40 per cent, above normal in 22 per cent. [One of us, W. B., has encountered abnormal excretion of hippuric acid only occasionally.—Ed.] The bilirubin excretion test demonstrated delayed excretion in 48 per cent. The galactose tolerance test was not sensitive enough to detect chronic or mild liver damage: it was abnormal in only 14 per cent. In 44 per cent of cases the icterus index was abnormal (above 8). Hypoalbuminemia was present in 68 per cent; an abnormal albumin-globulin ratio, in 76 per cent. No one test should be used as evidence for liver dysfunction. The azorubin S test was considered the best; when it indicated an abnormality, one or more other tests did also.

[It is impossible to interpret these data in terms of etiology because of the doubtful significance of the tests themselves and because the hepatic dysfunction varied in type, not always being a matter of delayed excretion. Since liver dysfunction was not present (by these tests) in all cases, what dysfunction there was must be regarded as perhaps the result, not the cause, of the disease.—Ed.]

Factor of Endocrine Abnormality. Metabolic rates were generally normal, occasionally abnormal (more often below than above normal).

Rates were normal in 60 per cent, subnormal in 35 per cent, above normal in 5 per cent of Potter's 60 cases. Noting that rates were higher among his clinic, than among his private cases Rawls[616] concluded that rates in ambulatory cases are 10 per cent higher than the true basal rates: "therefore all rates of 0 or below should be considered below normal." Thus he considered the great majority of cases to have subnormal rates. [It is difficult for us to accept this view.—Ed.] The rates bore a relationship to the activity of the arthritis; sedimentation rates and nonfilament counts were high in the presence of high metabolic rates, lower in cases of subnormal metabolic rates.

Neurogenic Factors. German workers[757] considered that in cases of atrophic arthritis toxins from infected foci attack the autonomic ganglia and the anterior horn cells of the spinal cord, producing in effect a type of chronic anterior poliomyelitis with muscular wasting and fibrillation.

Psychogenic Factors. Every practitioner can recall patients whose atrophic arthritis began after severe mental stress—the death of husband or wife, financial loss, etc. Some physicians think that this is coincidental, others do not.[87, 162, 539, 727]

From a study of 50 cases of atrophic arthritis (and a control series of 25 cases of varicose ulcers) Cobb, Bauer and Whiting concluded that environmental stress (poverty, grief, family worry) bears more than a chance relationship to the onset and exacerbations of atrophic arthritis. "The relative importance of these factors in the etiology of atrophic arthritis can be established only by a much more detailed psychiatric study."

Such a study was attempted by Booth who employed psychiatric tests and the Rorschach method and by Stein-Lewinson who analyzed the handwriting of arthritics before and after development of the disease (cases in which arthritis attacked the writing hand were excluded). Stein-Lewinson studied 31 cases of atrophic and 24 of hypertrophic arthritis but did not analyze the two groups separately. "The arthritic is fundamentally a weak person who overtaxes his inadequate amount of aggressive energy to a considerable degree, distributing it in a disproportionate manner." Certain characteristics are present in his pre-illness handwriting and persist through the disease: they indicate an inadequate vitality which is overstrained by the desire of the patient to hide his weakness. Features which appear after the onset of his disease indicate a breakdown of will power, masochistic sensuousness, hypocrisy, irritability and lessened adaptability. Booth analyzed 45 cases of "chronic arthritis" [types not stated, presumably the same 25 cases of atrophic and 18 of hypertrophic arthritis noted before[5] plus two new cases.—Ed.] The arthritic's basic characteristics include a predominant instinctual urge to act, susceptibility to influence by environment, a strong consciousness of the laws of behavior of the original environment which leads to sharp restrictions of the active impulses, and a fear of emotional frustration. This personality attitude makes his adjustment difficult and creates a defensive attitude. In summary there was "a remarkably consistent picture of a certain typical dynamic constellation which could be found in all arthritic patients, notwithstanding great psycho-somatic differences in many other respects."

[Neither Booth nor Stein-Lewinson made any attempt to separate the cases of atrophic from those of hypertrophic arthritis. When one considers that the former cases represent a much younger age group, doubtless with greater financial worries and crippling, a group whose lives are "ruined" in their prime and that the latter patients are older, have probably lived full, often successful lives and are only moderately disabled physically and financially, it is difficult to see how any combined analysis of the groups could be other than most general and probably erroneous. It probably represents a psychologic study of so many "sick people," not so many "arthritics." No control cases were studied.—Ed.]

In view of these studies the observation of Gregg that psychotics are relatively immune to arthritis seems strange at first. In Massachusetts one out of every 36 persons in the general population had chronic rheumatism (Bigelow and Lombard, 1933), whereas only one out of 610 psychotics had arthritis. Thus arthritis is 17 times less frequent among psychotics than among others. In 3000 necropsies in psychotic cases "no frank arthritic joints" were found. The "largest arthritis clinic in Boston" has only transferred one of 5766 arthritic patients to the Boston Psychopathic Hospital.

Without extolling the advantages of becoming psychotic, Gregg explained thus: Man is endowed with reactions that enable him to escape from or fight off noxious forces (by increasing his blood pressure, pulse, blood sugar, alertness, etc.). These reactions are beneficial when they occupy the usual stimulus-reaction span of time. But if this stimulus-reaction span of time is unduly prolonged, the result is injurious. Man through his memory and imagination has lengthened the period during which the muscles are tense, the blood pressure raised, etc. These "normal reactions," if unduly prolonged, may produce an increased ischemia of muscles furthering infection and resulting in such conditions as hypertension, angina, gastric ulcer, spastic colitis and arthritis. In childhood and among the feeble-minded or psychotics, imagination and memory have not yet developed, do not develop fully or retrograde. Therefore certain diseases closely related to emotional stress are statistically rare. Thus among psychotic patients without a prolonged stimulus-reaction span, because of impaired imagination and memory, there is little prolonged muscle tension or drag on the joints, little setting of the stage for prolonged ischemia, malnutrition, or infection of joints, and therefore chronic arthritis is rare.

Conclusions on Etiology. Unfortunately this can be very simply stated: nobody knows the cause of the disease.

Relationship between Atrophic Arthritis and Other Diseases

Rheumatic Fever. English and American physicians are more likely to regard atrophic arthritis and rheumatic fever as separate entities than are Germans and Scandinavians, many of whom think that the two diseases have a common etiology and that atrophic arthritis often results from rheumatic fever.[757] Regarding both as manifestations of allergy Levinthal and Pagel considered them closely related. But after comparing the connective tissue reactions of the two diseases Collins [177] noted enough differences to state, "If experienced clinicians are prepared to dissociate [the two diseases] the pathologist is not yet in a position to dispute them."

Treatment of Atrophic Arthritis

General Remarks. According to their attitude on the treatment of this disease physicians can be classified as (1) the pessimists or nihilists, (2) the optimists and wishful thinkers, and (3) the realists. The pessimists regard all current treatment as essentially useless or merely mildly palliative; on behalf of a patient they may make one therapeutic gesture (usually tonsillectomy, or salicylates probably given intravenously) and when that fails, they say to themselves, "What's the use?" and pack the patient off to a spa or a "rubber." The optimists or wishful thinkers are often, for a time at least, highly successful with their patients. Their radiant optimism is

infectious and serves as potent psychotherapy, but they too often oversell themselves to their patients who expect more than the physician can deliver. These optimists also are in danger of overselling themselves on some remedy and thus becoming faddists. The realist knows full well how inadequate current methods are, how far they are from a truly satisfactory and specific or relatively specific method of treatment, but he also realizes that, while zealously hunting for new tools, he must for the sake of today's patients use today's remedies as vigorously as possible, since thereby he can do much to relieve pain and to prevent or control deformities.

Some recent generalizations on treatment included the following: "Probably no part of medicine is more impotent than that which deals with arthritis," wrote Creer. "Our orthopedic clinics are littered (I can think of no better word) with such cases." The arthritic patient is, "generally speaking, badly treated in the long run, either because the average physician considers the condition unworthy of exhaustive treatment in the beginning or considers it hopeless when well developed" (Wheeldon). "The enthusiastic neophyte tries first, the panaceas described in the best medical journals, next those noted in ordinary medical journals and then quietly sanctions the use of the miraculous cures found in any daily newspaper" (Weinstein). Although no specific remedy is yet available the intelligent application of the best of current methods is productive of worth-while results and patients should not rely on "nature" to stop the disease. "Some patients believe that arthritic pains, like the wicked will flee when no man pursueth but we can assure you that they make better time when the doctor takes after them" (Wyatt and Thompson).

One physician [810] was "unhappy because many of those who are qualified to write on arthritis have been somewhat pessimistic in their attitude toward newer remedies with the result that the family physician accepts the fact in his own mind that nothing new is of benefit. . . . A spirit of optimism—even though conservative—should be developed in the family physician." But the physician's optimism must not be such as would give rise to a conversation recently quoted in an editorial [248]: "Doctor: 'Well, you've had 3 months' treatment. How are you?' Patient: 'About the same, Doctor.' Doctor: 'But surely you feel a little better after all the trouble we've taken?' Patient: 'Well, Doctor, I'm sure I'm very grateful. Perhaps I do feel a *little* better.' Doctor: 'That's splendid! I felt sure you would.' (Writes on record, 'Improved.')"

"Between a strong therapeutic nihilism on the one hand and wishful thinking on the other, there is a middle ground in the care of arthritics, within which many experienced students and clinicians find cause for great optimism," according to Pemberton. Studies on the effects of jaundice and pregnancy show that the pathologic physiology of atrophic arthritis is more rapidly reversible than was previously supposed. The physician treating arthritis has "already available many, sometimes all, of the varied mechanisms necessary to a true reversal of the disease." But he takes his thera-

peutic cue from those studying the disease and "unless a reasonably wide-angled, and above all, coördinated program be presented to him, he cannot be blamed if he turns from academic negativism to the samples sent him by the drug house." [592]

Physicians now realize that until more is known about the natural course of the disease, it is impossible to forecast the particular course which a given case will follow, and equally impossible to evaluate any given treatment (Duthie). The truism "Experience is fallacious, judgment difficult" is especially applicable to a study of the results of treatment in atrophic arthritis. In this disease, the natural course of which has never been adequately mapped out, its chronicity, its irregular tendency to spontaneous remissions, the ineffectiveness of therapy in the more relentless cases, all contribute to the problem of evaluating therapy. The skeptic properly discredits many apparently good results with the assertion "it might have happened anyway." Only when therapeutic results follow some definite uniform pattern which does not occur consistently among any large number of untreated patients can this argument be refuted (Anderson, Lamb, Barritt and Nerb). The Council on Pharmacy and Chemistry [208] suggests that physicians, trying to evaluate remedies for arthritis, use the methods employed by the Council in assessing the worth [or rather, the worthlessness.—Ed.] of sulfur. Before accepting a remedy as valuable "satisfactory evidence must be produced that sufficient controls have been employed and that follow-up periods of sufficient length to rule out spontaneous remissions have been observed. Further, the types of cases in which the preparation may be used with fair expectation of benefit must be determined, and their chief contraindications, optimal dosage and best form and route for use must be defined."

Management of Foci. The year's comments on focal removal produced no new or different ideas on the subject, merely a different set of authors. Since the infectious theory remains unproved, since the removal of an infected focus is rarely the sole form of therapy and is only occasionally followed by prompt improvement, the whole matter remains controversial. A patient with atrophic arthritis and infected foci is in a "less fortunate position" than one with arthritis alone; hence genuine foci of sepsis should be removed.[310] The medical profession is generally, if unenthusiastically, agreed on this.[263] But there is disagreement as to the optimal time for their removal: according to some, selection of this time requires considerable nicety of judgment. One view is that "the patient must first be rested and built up" [263]; another is that delay is generally unnecessary (except in the presence of acute tonsillitis) and the results of prompt removal are "better than if one temporizes with an ineffective program of building up resistance first." [542]

[Five of us favor the removal of infected foci without delay unless the patient is seriously ill; two of us postpone removal until after a preliminary "build-up." None of us advocates removal of foci as a specific remedy but only as a measure that may improve the patient's general health.—Ed.]

Articular exacerbations which occasionally occur after a focus is removed are "unfortunate" but generally transient and unimportant.[263, 542]

[We rarely see more than an occasional transient, unimportant flareup.—Ed.]

The removal of infected teeth was approved.[263] Some urged the removal of pulpless teeth,[263, 631, 755] others did not.[542] Removal of roots not obviously (i.e., roentgenographically) infected was not approved.[135] Cogan considered the treatment of gingivitis more important than that of infected teeth. But cures following dental extraction are the exception, not the rule. A small percentage of the patients of Vaizey and Clark-Kennedy "appeared to have had a beneficial effect" after alveolectomy for rheumatism, but of 126 patients who had had all their teeth out for purely dental reasons, nineteen later had rheumatism. Fantus urged that tonsils be removed "regardless of their appearance." [Some of us do not agree.—Ed.] Monroe approved this practice for patients under 30 years of age, but urged more discretion in older persons. Hamblen-Thomas believed that the conservative, and if necessary the operative, treatment of sinusitis improved or even "cured" many arthritic patients; but "from bitter experience" Shackle left antrums alone unless they definitely retained pus. Results in the 12 cases of Williams and Slocumb in which sinuses were operated on were not very impressive: six of the patients noted relief, but four of these also had their tonsils removed. Although lateral sinus thrombosis complicating ear infection usually produces acute pyemic arthritis, Asherson considered it a possible cause of chronic arthritis also.

Vaccines, Antigens, Filtrates. Crowe and his colleagues continue to be enthusiastic advocates of vaccine therapy.

Crowe again described his general plan of vaccine therapy [205, 206, 207] and reported results. Of 212 patients with atrophic arthritis 5 per cent became symptom free, 35 per cent were much improved, 41 per cent were improved, 19 per cent were unimproved. Of 107 patients with "active infective arthritis" 12 per cent became symptom free, 31 per cent were much improved, 38 per cent were improved and 19 per cent were unimproved.

Crowe's vaccine was used by Bunting and by Voss. Of Bunting's 60 patients with rheumatism (type unstated) 13 were cured, 14 much improved, 25 improved, and eight unimproved. Results required "months, not weeks" of treatment. Of Voss' 86 patients 16 were "cured or very much improved," 36 were improved, 34 were unimproved. Weinstein's results with Crowe's vaccine were "disappointing" (no details).

[We cannot share Crowe's enthusiasm for his or for any other vaccine.—Ed.]

Anderson and his colleagues [21] treated 170 patients with autogenous streptococcal filtrates based on tests of skin and joint sensitivity thereto. The less marked the skin or joint sensitivity the better the results: 23 per cent became symptom free, 5 per cent almost symptom free, 30 per cent markedly improved, 28 per cent slightly improved, 14 per cent unimproved. Reeves enthused about his results from streptococcal antigens selected on the basis of skin sensitivity: when treatment was begun within the first eight weeks of symptoms, "This treatment has not failed in any case." [This is difficult to believe. No details were given.—Ed.] Weiner gave pooled arthrotropic streptococci intravenously in 31 cases. Improvement was marked in none, moderate in seven, transient in 13, absent in 11. Vaccine made from a nonpathogenic air-borne bacillus was used in control cases. When given intravenously in 12 cases (with mild fever reactions) improvement was marked in none, moderate in four, transient in seven, absent in one; when given subcutaneously (without reactions) in 20 cases, improvement was marked in none, moderate in four, transient in seven, absent in nine. Weiner concluded that the streptococcal vaccine was nonspecific and that results are

better when febrile reactions are induced. This was also the opinion of Howitt whose results with vaccine were "unimpressive" (no details).

Reductions in the leukopenic index during vaccine therapy were regarded by Hicks and Wyatt as indices of the amount of desensitization accomplished. Burbank still considered vaccine therapy the best single form of treatment (no details), but Shackle considered vaccine "useless." According to Armstrong there is no standard dose or plan of increasing doses: individual dosage is the sine qua non of vaccine therapy.

Results with vaccines have disappointed most European physicians, who consider them nonspecific and relatively ineffective except as a form of psychotherapy. Having observed their use in many American and European clinics, Tegner concluded, "In the present state of our knowledge of the etiology of rheumatism in general, and of rheumatoid arthritis in particular, the use of vaccines cannot be either endorsed or rejected."

Foreign Proteins. Results therewith were no better and no worse than those with "specific" vaccine, and inferior to chrysotherapy.[410]

Autohemotherapy. Ishmael reported that autohemotherapy (10 to 20 c.c. blood) "reinforced" with artificial fever (101.5° F. for one hour, using inductothermy for adults and typhoid vaccine reactions for children) provoked "complete remissions" in all of seven cases of juvenile Still's disease. Results in atrophic arthritis of adults were less notable; among 10 cases, a complete remission resulted once, improvement in four; no improvement in five. Combined therapy was superior to either alone.

Chaulmoogra Oil. Unusual results, at times "truly astonishing," were reported by Stanley. Of 23 cases of atrophic arthritis thus treated results were "100 per cent complete relief" in almost 40 per cent (nine cases), marked (80 to 95 per cent) relief in 26 per cent (six cases), moderate (50 to 75 per cent) relief in 17 per cent (four cases), less marked in the rest (four cases). Patients cured received from one to 45 injections (each 1 to 5 c.c.) intramuscularly. Reactions lasting 24 hours were often produced (fever, headache, malaise, sometimes severe urticaria). Results were less notable in cases of mixed or of hypertrophic arthritis. "Sterile abscesses" occurred in 8 per cent of the cases.

[In view of the experiences of others it is difficult to accept this evaluation. No wonder reprints of this report were circularized (with the title changed) to extol the virtues of a commercial preparation of chaulmoogra oil. The originator of this method of treatment has never made a second report on it.—Ed.]

Bee Venom. Various types of acute and chronic arthritis were treated with bee venom by Ainlay. Of 37 patients 12 had atrophic arthritis. Results which were not analyzed separately follow: 16 were "cured," 16 relieved of pain and the swelling reduced, four improved, one was unaffected. "Thirty-one of our cases have not had any venom for over two months and are still relieved. . . . The one complete failure turned out to be a parathyroid disturbance with muscle spasm and bony deformity." [This report is unimpressive for various reasons, chiefly the unclear method of tabulating results and the short (two month) follow-up. One of the discussors of this paper asked, "Is this an advance in the treatment of rheumatic disease, or is it just another treatment?" Our answer would be the latter.—Ed.] Others [255] vaguely approved such therapy but Mackenna, an advocate of bee venom therapy of fibrositis, considered it valueless in atrophic arthritis and had "long abandoned it."

Diets. No really new data appeared but a few comments are reportable. The use of a diet deficient in calories for a few days may induce striking changes in some cases of atrophic arthritis, but in more cases not only inconvenience but definite harm has resulted.[32] There is no scientific

distinction between "red" and "white" meat.[32] Of 11 patients given 100 gm. of glucose daily with an "ordinary hospital diet" seven were "definitely worse during the time [unstated] they were taking the glucose, and only one of these eventually showed improvement in the sedimentation rate on leaving" (Yeoman). But Miller and Wilson were "not convinced that the so-called Pemberton diet is beneficial in a large majority of cases." Avoidance of "acid items" of diet (tomatoes, oranges, lemons) is harmful, not beneficial, since they are the chief sources of certain essential vitamins. They do not make the body more "acid" or produce an "acid-state." The acids in these foods are only weak organic acids, like citric and malic acids; they are easily oxidized in the body, and their basic elements appear in blood as alkaline carbonates. Hence these "acid foods" actually serve as available alkali.[539]

The supposed analgesic effect of a "raw vegetable diet" (50 per cent raw fruit and vegetables plus cereal and milk)[4] results not from its high vitamin C content (as some have contended[5]) but from its altered salt-potassium ratio, according to Pillman-Williams. The diet's content of vitamins A and C and of potassium is high, of sodium low. Such a diet produces analgesia and loss of weight; effects not obtained from ordinary diets plus vitamin C in massive doses, or from the cooked or uncooked diet with added salt.

[The diet was not considered specific; it was used also in cases of hypertrophic arthritis and of fibrositis. No statistical results were reported.—Ed.]

Vitamins. The current frenzy of many physicians is to find the right antirheumatic vitamin.[117] Chronic arthritics do frequently exhibit deficiencies of vitamins in their diets or serums or both. Such deficiencies lessen resistance to infection, and infections apparently lessen utilization of vitamins. Hence diets adequate in vitamins are indicated in arthritis. But vitamin therapy is still in the experimental stage and is not yet a rational treatment. Most physicians[255, 263, 542] advocated the supplemental use of vitamins in ordinary (small) doses, especially cod liver oil and brewers' yeast, but the value of vitamins in massive doses is unproved.

Vitamin A. Some patients with atrophic arthritis are deficient in this vitamin,[255, 686] but Monroe considered vitamin A concentrates of no value.

Vitamin B. Diets in the cases of Sherwood and Thomson were rarely deficient in this vitamin, and neuritis was even more rarely seen. The vitamin is useful for anorexia and dyspepsia.[542]

Vitamin C. Whether their diets have adequate[686] or inadequate[353] amounts of this vitamin, most arthritics have subnormal amounts in serum. Therefore, Hall, Darling and Taylor gave their hospitalized patients with atrophic arthritis 200 mg. of vitamin C daily for eight months. Although the blood became saturated, no improvement attributable to the vitamin was noted.

Vitamin D. Farley again noted marked relief from the use of massive doses (50,000 to 700,000 U.S.P. units daily) of vitamin D (ertron), but he was almost alone in his enthusiasm. Terhune gave 200,000 U.S.P. units

(drisdol) daily for one to four months, then smaller doses (7,500 to 15,000 units) for at least six months. Most of his patients (numbers not clear) were not improved. In some cases subjective relief was noted but Terhune agreed with Abrams and Bauer [6] that no objective improvement resulted. No significant toxicity was noted; occasional gastrointestinal intolerances were controlled by brewers' yeast. To 35 patients with "arthritis" (types unstated) Andersen and Theis gave 150,000 to 250,000 U.S.P. (XI) units of viosterol daily for several months; only four were notably improved. Weinstein considered it "of no great value" (no details). Ellman's clinical results (no details) "did not support the theory of Dreyer and Reed." The good reports have been "based on uncritical enthusiasm" and there is no rationale for this treatment (Monroe).

It was agreed that the dangers of toxicity have been overemphasized.[19, 266, 758] Using viosterol in doses stated above, Andersen and Theis noted no hypercalcemia and no significant or consistent alterations in serum calcium, phosphorus or phosphatase. But such therapy generally decreased the serum phosphatase in the cases of Smith, Klein and Steck, especially in those in which ultimate benefit ensued. In Farley's cases ertron generally caused no significant toxicity or changes in serum calcium. According to him other forms of vitamin D generally elevate the serum calcium, may produce toxicity, but may not give relief. He blamed toxicity on the method of activation of the vitamin. "This vitamin D preparation [ertron] is activated from ergosterol by means of an exclusive method (Whittier process), hence differs from the type of vitamin D used by Abrams and Bauer." Therefore the poor results reported by Abrams and Bauer [6] "are applicable only insofar as the type of vitamin D they employed is concerned and are possibly not applicable to vitamin D obtained by any other process."

[Farley had no control series to support this statement. Others have used ertron without significant results, and, as noted above, other preparations have been used without significant toxic reactions. Certain preparations, notably ertron, are now being advertised vigorously, one might say, offensively, in view of their glowing claims. This therapy is rather expensive when long continued and it is the considered opinion of most of us that it is not worth the money. However, one of us, W. P. H., believes that such therapy will occasionally produce a notable remission and that further work with vitamin D should be done under adequate control in large clinics.—Ed.]

Vitamin G. Dietary deficiencies in this vitamin were common in the cases of Sherwood and Thomson, but no results of therapy were reported.

Intestinal Therapy. Those (rather few) physicians who consider the "reduction of intestinal toxicity" possible and important approved the following: preparations of belladonna for "colon spasm," [275] paraffin oil, other bulky substances, or hot fomentations for constipation or diverticulosis,[275] potassium permanganate enemas,[325] colonic irrigations.[275, 325, 710, 826] Commenting on the latter Patterson stated, "Certain patients are morbidly interested in bowel contents and in these the psychological effect of a good 'decarbonizing' is the chief factor in improvement. It is useless to argue with this type of patient, since, like the advertisement for Pear's soap: 'he won't be happy till he gets it!'"

[We suggest reasoning, rather than arguing, with such patients. There is no satisfactory evidence that the abnormalities and structural irregularities of the colon, sometimes (but not always) seen in weak, emaciated arthritics, are the cause of the

disease. In cases of undoubted classic forms of intestinal disease (typhoid fever, amebic and bacillary dysentery, ulcerative colitis, Hirschsprung's disease) articular symptoms develop with extreme rarity (incidence 0 to 4 per cent), and physicians with critical judgment have long since abandoned "colonic irrigations for autointoxication in arthritis" as not worth the time, trouble and expense.—Ed.]

Miscellaneous Medicines. The rôle of drugs, none of which could be regarded as specific, was discussed with the supposed indications for iodine, quinine, strychnine, calcium, iron, insulin (for anorexia and loss of weight), etc.[255] Salicylates, especially aspirin, are the most helpful of all as analgesics, but their use to mask symptoms, which thereby leads to the postponement of adequate treatments until the disease has made serious advances, was strongly condemned (Tegner). When aspirin produces too much sweating, the use of extract of hyoscyamus (0.02 gm. per dose) was recommended.[263] Sell reported a case of salicylate poisoning in an eight year old child with Still's disease; after 190 grains each of sodium salicylate and sodium bicarbonate had been given (within five days), sweating, vomiting, abdominal pain, rapid respirations, slight delirium and acidosis with acetone and diacetic acid in urine developed, but recovery followed appropriate treatment. Because of the acid character of ordinary aspirin and the toxicity it may produce, Green [335] recommended calcium aspirin as less toxic, less productive of "acid indigestion," more soluble, and quicker and longer in action.

For fatigue benzedrine sulfate, 20 mg. after breakfast and also after lunch, was recommended; arsenic was considered [255] of value in "improving the general tone" [whatever that is—Ed.].

Endocrines. The use of thyroid extract was advised for patients with low metabolic rates.[255, 616] Rawls said its results were "frequently good in *inactive cases* [italics are ours.—Ed.] of the Marie-Strümpell type."

[Good for what?—Ed.]

Estrogenic hormones were used by some.[255, 611, 828] The cases in which Yeoman used hydrotherapy plus progynon (10,000 units twice weekly) were the only group in which there was a consistent drop in sedimentation rates. Radnor reported the case of a woman aged 49 years bedridden after 10 months of "typical polyarticular arthritis" unrelieved by heat and gold. Because she had had flushing since the menopause six years before, he gave estrogenic hormone (50,000 units intramuscularly thrice weekly). Within two months she gained 13 pounds and was able to resume work; after two more months she was free of flushes and joint pain, joints moved freely and swelling was reduced (shown in photographs). No other treatment was used. When three days of menstrual bleeding occurred doses of stilbestrol replaced the injections.

Those Other "Remedies!" Here are some data on remedies investigated by the Council on Pharmacy and Chemistry and by others.

Causalin. This was discussed and condemned previously.[5, 6] It contains aminopyrine. An arthritic patient took over 100 tablets in four months and died of agranulocytic angina.[215]

Aciform II. This is advertised as containing formic acid, alcohol, iodine, sulfur and terpene to be injected at painful sites in cases of lumbago, acute and chronic infectious or traumatic arthritis, sciatica and neuromuscular pains. Among 78 cases of "arthritis" (types unstated) treated by Mayers and Livingston, "improvement" was "complete" in 33 per cent, marked in 43 per cent, slight in 19 per cent, absent in 5 per cent. [In the section headed "Rationale" the technic of administration and *not* rationale was discussed; data on the latter were notable by their absence.—Ed.] The Council on Pharmacy and Chemistry [196] caustically criticized this preparation as "of unscientific composition marketed under a coined proprietary name with exaggerated and misleading claims of therapeutic value. . . . Formic acid preparations can be dismissed from the armamentarium of pharmaceutic preparations without the slightest chance of depriving the sufferer from these [arthritis and associated] conditions of any possible relief."

Condemned as "fakes" were "Zorbit" and "Vita Minro Health Tablets" for arthritis, rheumatism, etc.,[120] and "Sal Trag" a remedy of secret composition formerly sold as Nue-Ovo; "there is at least one report of severe inflammation of both eyes, with a residual defect in a woman who had taken Nue-Ovo for arthritis." [247]

Transfusions. No new data were reported.

Sulfur Preparations. Wheeldon again,[3, 811] with Bosher, recommended sulfur injections. Ellman considered them of benefit in some cases when febrile reactions were induced. Others [804] wrote "sulphur therapy rests on an elusive theoretical premise that the sulphur content of hair and nails is low in some arthritics" but it is also low in pellagra, malnutrition and other diseases.[739, 804] Febrile and toxic reactions, sometimes alarming, were produced by the English and American preparations used by Fletcher.[282] Some patients showed "slight improvement" but others were "definitely worsened." After reviewing the literature on the subject (85 references) Comroe damned sulfur therapy with faint praise. Of 30 patients given colloidal sulfur (three brands, given intramuscularly, intravenously or both) only 20 per cent noted both objective and subjective improvement; 30 per cent subjective but no objective improvement, 50 per cent were not benefited. Determinations of the cystine content of nails were of no help in predicting which patients would improve. Of a group of controls given injections of a placebo, 20 per cent noted subjective (but no objective) improvement. His results with sulfur were "no better than and in many instances not as good as those obtained by other means." Hence its routine use was not advised.

[Those still inclined to try sulfur for arthritis should read the devastating blast of Freyberg, Block and Fromer at this therapy.—Ed.]

Gold. Chrysotherapy was approved in seven English reports [171, 207, 217, 255, 302, 410, 756] with general discussions but no data on new clinical series. The latter were given in three American reports.[452, 650, 711] Tegner reviewed concisely the European and English methods and results from gold.

Indications and contraindications. These were as in previous reviews. Amenable for such therapy are cases of active atrophic arthritis with elevated sedimentation rates, but not inactive cases. Cases of ankylosing spondylitis were considered less (but still) suitable by some, unsuitable by others. The remedy is not helpful in hypertrophic or the specific arthritides or in fibrositis and is contraindicated for patients with atrophic arthritis who have, or have had, hepatic or renal disease, hemorrhagic diathesis, anemia, ulcerative colitis or chronic skin diseases (except psoriasis which responds well).

Results. "Cures" or marked improvement has occurred rather consistently in 60 to 70 per cent of English and European cases.[650, 756] American results have been consistently less striking, either because of greater conservatism in their appraisal, or the tendency to use gold in fewer early and more late, resistant cases, or to use smaller, less toxic doses. Key, Rosenfeld and Tjoflat treated 53 patients with myochrysine. The disease of only 6 per cent was "arrested"; 34 per cent of patients were improved "markedly," 25 per cent moderately, the rest little or not at all. Snyder, Traeger and Kelly gave gold sodium thiosulfate to 50 patients with these results: 2 per cent were "cured"; 10 per cent obtained "good," 36 per cent "fair," 52 per cent "poor" results. Results in 80 cases of Sashin, Spanbock and Kling who used mostly gold thiosulfate, in some cases colloidal gold-aurocein (sulphydryl-gold-naphthyl-trisulpho-carbonium derivative) were: cures apparently none, "very marked improvement" in 44 per cent, "moderate or slight improvement" in 39 per cent, no improvement in 17 per cent. Of these 80 cases 11 were of atrophic spondylitis. Improvement was marked in 45 per cent, moderate in 10 per cent, absent in 45 per cent. Thus the results, like those noted abroad, were inferior in spondylitis to those in cases of involvement of peripheral joints.

Results in early cases were notably better in one series[711] but not in another.[650] The effect of chrysotherapy on sedimentation rates was studied. Snyder, Traeger and Kelly did not always find sedimentation rates a reliable index to clinical improvement. Rates were actually higher after, than before, treatment in 47 per cent of the improved cases, and were lower after treatment in 80 per cent of the unimproved cases. But a notable decrease in sedimentation rates was seen in most of Goldie's 400 cases, and clinical improvement was generally proportional to the decrease. The extent of the reduction was entirely determined by that occurring during the first course. But no relationship existed between the initial rate and the clinical result, and determination of the rates was of *no value* in anticipating toxic reactions or clinical relapses.

Dosage. Different plans used abroad were discussed[171, 207, 756]; dosage varied notably. According to Tegner, Van Breemen's maximal individual dose was only 20 mg.; maximal total dose for a course only 500 mg.; Secher's initial dose was very large, 500 mg., but massive doses of vitamins reputedly prevented toxic reactions. The usual European and English plan was that of Forestier: individual doses up to 150 or 200 mg., total dose for a course 1.5 to 2 gm., two or more courses being given. Tegner's own scheme was doses of 10, 20, 50 and thereafter 100 mg. until a total of 1 gm. had been given; injections were given four to seven days apart and two courses, six to eight weeks apart. Ellman again[6] reviewed his two schemes: one of large total doses (2 to 2.5 gm.) given to institutionalized patients with high sedimentation rates; one of small total doses (10, 20, 40, 75, thereafter 100 mg. each dose; total

dosage, 1 or 1.5 gm.), for two or three courses six weeks apart. According to Crowe, Irvine, Coke and Beauchamp [171, 207] set time schedules for successive and increasing doses are bad; doses should be small, not necessarily increased, and should be repeated sometimes days or weeks apart only when the remission after each dose has ended. Their plan of dosage was not stated clearly but depended on changes in their special differential sedimentation test.

The American plans were these: myochrysine, for adults a first dose of 50, thereafter 100 mg. weekly, until a total of 2 gm. had been given, then a second course in six weeks; for children an initial dose of 12.5 mg., thereafter 25 mg.[452]; gold thiosulfate, first dose of 25, thereafter 50 mg. once or twice a week until a total of 1 gm. had been given [650]; gold sodium thiosulfate, 5, 10, 15, 35, 50, thereafter 100 mg. until a total of 1 gm. had been given, with two courses six or eight weeks apart.[711]

Toxic reactions. These were as before: mild to marked erythema, exfoliative dermatitis, stomatitis, colitis, diarrhea, vomiting, transient albuminuria, hepatitis, aplastic anemia, eosinophilia, agranulocytosis, bronchitis, conjunctivitis, chills, fever. Sensitive persons may have these after a few doses, others toward the end of a course, or even later.[756] Toxic reactions occurred in 63 per cent of the cases of Key et al. (108 reactions in 44 cases; reactions were mostly mild, but four were severe: exfoliative dermatitis in three cases, agranulocytosis in one; no deaths); they appeared in only 15 per cent of the cases of Snyder et al. (no deaths but edema of the glottis necessitated tracheotomy in one case); of the cases of Sashin, Spanbock and Kling local reactions (joint pains) occurred in 25 per cent, other reactions (generally mild, severe in three, fatal in no cases) in 24 per cent.

Prevention of toxic reactions. Weekly tests of blood count, sedimentation rate, urine and weight should be made to note impending toxicity.[255, 756] Some [452] advised stopping treatment temporarily if leukopenia, eosinophilia, dry skin or pruritus occur. The prophylactic value of calcium gluconate was asserted by Ellman, denied by others.[452, 711, 756] In an attempt to prevent toxic reactions high carbohydrate diets, liver extract and vitamin C were used by some [452] but vitamin C was considered valueless by others [711]; intradermal injections of test doses and patch tests were of no value in detecting hypersensitive patients.[452] Coke claimed to be able to select cases properly and to prevent all serious toxic reactions by controlling treatment with repeated differential sedimentation tests.

Significant reductions in platelets may denote toxicity with danger of hemorrhage, according to Gasking; hence he urged platelet counts between each dose. The average normal platelet count for males is 351,000 (238,000 to 471,000), for females 398,000 (238,000 to 551,000). There is a normal average variation of 20 per cent. Counts in 20 cases of atrophic arthritis were normal (average total was 380,000; average transient variability, i.e., reduction, 18 per cent). Within three or four days of the first dose of gold the platelet count always decreased notably (average fall 35 to 50 per cent during a course). In some cases counts became stabilized or even increased to normal or above normal (accommodation reaction) but in other cases they continued to decrease. Hemorrhage can occur without thrombocytopenia, but is very likely to occur if platelet counts approach 40,000. Gasking cited a case of Forestier in which fatal cerebral hemorrhage occurred when platelet counts fell to about 30,000. Gasking recommended that small doses of gold be used and given not oftener than every seven days to give the platelets a chance to recover between doses. Treatment of patients whose initial count is 250,000 or less must be cautious; otherwise counts may fall to dangerous levels. The daily use of four oranges did not prevent the reduction of platelets, but the use of vitamin C ("cantan") apparently lessened the reduction by an average of 14 per cent.

Treatment of toxic reactions. Irritations of skin or mucosa "improved rapidly"

from the daily use of 150 to 300 mg. of nicotinic acid. Calamine lotion or colloid baths were used for pruritus, sodium thiosulfate for exfoliative dermatitis, pentnucleotide for agranulocytosis.[452]

Mode of action. The bactericidal effect of gold is supposedly negligible.[463] Although most gold preparations contain sulfur the amount of the latter is too small to produce results.[711] It is the gold which is effective; preparations of gold without sulfur are effective although sulfur may be an adjuvant.[171] The mode of gold's action is not known: it may produce mild but prolonged shock therapy, stimulating reactions to toxins.[756] It may be a "catalytic stimulator" of the reticuloendothelial system or of the general defense mechanism. In normal animals gold is deposited in the cells of the parenchyma of many organs (especially liver, spleen, kidneys and bone marrow), but in animals with chronic infections it is deposited almost entirely in the cells of the defensive reticulo-endothelial system.[171, 463] Synovial membranes contain numerous reticulo-endothelial cells; such cells in normal animals contain little gold, but in infected animals and in cases of synovial effusion with atrophic arthritis they contain much gold, according to Kling and his associates. Overdosage may poison the very system one is trying to stimulate; hence dosage should be planned to "maintain the minimal catalytic quantity necessary and that will need replacement as the physiologic elimination of gold occurs" (Coke).

Conclusions on the value of chrysotherapy. It is not a cure-all nor should it be adopted as a general measure, according to Tegner. Because of its toxicity it may not be here to stay, but when properly handled, it is a valuable, simple method of treatment available to ambulatory patients; it will often stop or notably affect the disease, not in six years but in six months.[756] Davidson was unwilling to accept unreservedly current claims for chrysotherapy. It should not be used to the exclusion of orthodox measures.[217, 302] It is not a safe procedure, but it is worth the risk.[452] According to Goldie, every patient should be given the opportunity of benefiting from this treatment at the earliest stages. Sashin, Spanbock, and Kling considered it superior to any other present method, but still not the ideal remedy; it will not always stop the disease in early cases. Snyder, Traeger and Kelly were less optimistic: their results were not as good as those reported abroad: it is "too dangerous for general use," and only suitable for patients unrelieved by older remedies.

Vasodilators: Histamine, Choline. Of the 78 patients to whom Kiel gave acetyl-beta-methylcholine chloride (mecholyl) by iontophoresis 55 per cent were "completely relieved," 33 per cent partially relieved, 12 per cent not relieved.

[These statistics do not jibe with Kiel's more modest conclusion that "end results in the rheumatoid group are encouraging." There is no treatment of any sort which has consistently "completely relieved" anywhere near 55 per cent of such patients. We suspect that the writer was in a more properly critical frame of mind when he wrote his conclusion than when he made his table.—Ed.]

Similar treatment was given to 35 arthritics (types unstated) by Boyd, Osborn and Markson. Increased mobility and decreased stiffness and pain were sometimes noted. Ellman vaguely approved the use of histamine, thio-histamine or acetylcholine. Histamine by iontophoresis seemed better

than by inunction.[462] But histamine therapy was "disappointing" to Weinstein.

[These remedies have fewer advocates each year. Current reports were unimpressive.—Ed.]

Sulfanilamide. Large doses for 8 to 27 days failed to produce any effect in 10 cases of Coggeshall and Bauer but presumably improved three cases of Traut and Logan.

Bile Salts. "The majority of arthritics have some liver dysfunction and mild stimulation of the liver with bile salts is advantageous" wrote Burbank. Collins[182] regarded as "satisfactory" her results with bile drainage and injections of decholin (details meager).

[One of us, P. S. H., has recently[877] reviewed the generally poor results of others from decholin; its use in his own cases was ineffective.—Ed.]

Rest and Movement. Rest is "the most useful single basic factor in treatment," but it is not a single entity; it is "a mosaic of countless components, some of which may do harm." The "doctrine of rest" does not conflict with the need for nontraumatizing motion of joints at the proper time and in proper amounts.[592, 781] An ingenious water bed to prevent bedsores and hypostatic pneumonia of bedridden patients, was described.[261]

Physical Therapy. Current articles on the use of various types of physical therapy in arthritis contained little that was new. Students of rheumatism should read Tegner's description and appraisal of methods used in various American, English and European clinics and spas. The importance of physical therapy was everywhere recognized but there were "emphatic" differences of opinion as to the most suitable form for different conditions. Physicians must not buy one machine and use it in all cases; one must choose that type of physical therapy which will give the most relief to the individual patient.[468] Every therapist should have a "museum room where discarded apparatus in which we once had faith may be placed and catalogued. This would forever furnish a lesson in humility" (Heyman[304]).

Some general articles on the latest developments in physical therapy appeared.[203, 470, 471, 502, 532] The case for infra-red irradiation was presented,[776] but it has recently been shown that even the most penetrating infra-red rays are largely absorbed by the skin.[471] The advantages and contraindications of short wave as contrasted to long wave "conventional" diathermy were debated.[113, 243, 375, 469] There is no great difference between the two forms, but "short wave diathermy" apparently produces deeper, more uniform heating and is more readily applied.[193, 195, 473] Fangotherapy is helpful, but inadequate as a sole means of treatment.[787]

Further data on the optimal method of using contrast baths were reported by Collins, Ernst and Woodmansey. These were summarized in last year's Review. In England best reactions were not obtained with the usual one minute hot, one minute cold, one minute hot technic, but with a cycle of eight minutes hot, three minutes cold, or six minutes hot, two minutes

cold. In America (where patients tolerate cold less well than in England) the best technic was five or six minutes in hot water (about 113° F. or 45° C.) and not over two minutes in cold water (about 45° F. or 7.2° C.) alternating back and forth for 30 to 40 minutes, beginning and ending in the hot water.[470, 471]

The urgent necessity of supplementing professional physical therapy with home treatments was again stressed. "A thirty or forty minute baking or a short wave treatment three times a week will cause very little or no increase of the circulation of fingers, but if this is supplemented by home treatment with hot packs, heating lamps or other measures, much more adequate treatment is rendered."[308] Coulter stated that physical therapy once daily is insufficient; it should be applied at short intervals during the day. Simple methods for home treatment were outlined.[194, 470]

The effects and technic of massage[54] and also the advantages of various types of hydrotherapy[244, 470, 590, 593] were reviewed. Hydrotherapy is not indicated in cases of febrile atrophic arthritis.[590] To ascertain the proper type of hydrotherapy for a given patient the capacity of his skin to perspire must be studied. When in doubt the milder forms of hydrotherapy should be selected until the evidences of free lymphatic circulation and prompt skin reaction warrant the use of stronger forms. "Bath crises" ("getting worse before getting better") can thus be avoided.[593] The special advantages of spa therapy were presented.[38, 116, 393]

Undergraduate education in physical therapy is too meager; the average in 66 medical schools was only 10 hours in contrast to the 30 hours considered the requisite minimum by the Council on Physical Therapy.[212, 656] The acceptable schools for physical therapy technicians and their essentials were listed.[401, 402, 403]

Climate. A trip to some "salubrious resort" is beyond the means of most arthritics; were the patient to go there he should stay at least six months or longer; therefore it is fortunate that "a good climate is only a pleasant luxury in the treatment of arthritis" and that "most patients can recover in their native atmosphere, if they have the determination and proper care" (Monroe). Having seen the results of treatment in many diverse climates, Tegner agreed with the foregoing. Arthritic patients (except those with traumatic arthritis) "almost invariably do badly" during sea voyages; acute exacerbations can occur as a result of the constantly varying atmospheric humidity; it is not equable, changing daily, sometimes even hourly (Elder). But changes in humidity and temperature are less important than changes in atmospheric electricity; symptoms increase in the presence of positive charges, decrease with negative charge. Thus the effect of storms varies because the electrical state of the atmosphere is quite as often negative before a storm as after, and may change rapidly according to Monroe.

[No data were given to support these statements.—Ed.]

Occupational Therapy. The value of this therapy combined with physical and other procedures is being recognized more widely. It provides physical and psychologic effects of real importance.[117, 608, 619] Two English visitors were "greatly impressed" by results of such therapy and by its

wide use in America.[238, 757] Approved American schools of occupational therapy were listed.[401]

Roentgen and Radium Therapy. Scott again strongly recommended local and widefield roentgen therapy. In atrophic arthritis local irradiation was used for palliative purposes, widefield irradiation for its constitutional effects. After local irradiation "possibly 20 per cent do well [but] the number of unsatisfactory results is disconcerting." From widefield irradiation "results are best in the acute rather than in the chronic stages. The effect is frequently delayed 2 or 3 months." Technic was described. [It is difficult to believe that any result "delayed" as long as two or three months is due to roentgen therapy.—Ed.] Eidenow's appraisal was pessimistic: atrophic arthritis is only benefited if treated early; small doses of the medium wavelength gamma rays were preferred to larger doses of hard roentgen-rays of short wavelength. Tegner noted that radiologists were more enthusiastic about roentgen therapy than were their clinical colleagues. Radon was considered of no value.[388]

Fever Therapy. No enthusiasm for this treatment was recorded. Neymann recommended fever sessions (104° F. for eight hours) in early or more acute cases but gave no results. A few fever sessions were considered useful in enhancing articular circulation prior to orthopedic operations.[425] Ferderber recommended a course of fever therapy each spring and fall, but it was difficult to evaluate his results as he had a separate column each for "chronic atrophic," for "rheumatoid," for "acute infectious (non-gonorrheal)" and "chronic infectious (non-gonorrheal) arthritis." Fever therapy reputedly "reinforced" the effects of autohemotherapy in Ishmael's cases. Bromberg's results were "discouraging": only four of 12 patients were improved. Other results were as follows: in one group of 71 patients 11 per cent were "relieved," 69 per cent were "improved," 20 per cent were not[219]; in another group of 10 cases improvement was notable in only five.[347] Weinstein considered it "of little value." Elkins and Krusen[253, 470] did not advise the use of long fever sessions (only 20 per cent of patients thus treated were notably improved), but favored short (30 minute) sessions of fever (101 to 102° F.) every day or so during acute exacerbations, either in a Hubbard tank or fever machine (technic given).

Sympathectomy. This procedure can relieve pain and "improve circulation" but cannot of itself stop the disease.[585] Selig performed this operation in one case some years ago; death occurred two days after operation.

Nonsurgical Orthopedic Methods. Usual methods to prevent deformities and relieve muscle spasms were discussed.[139, 278, 340, 408, 679, 781]

In the presence of active inflammation over-exercise produces muscle spasms which may cause deformities; to prevent this rest should be provided by applying light removable splints early before deformities occur.[408, 598] But Hilton's dictum of "rest for pain" must not be overdone, or ankylosis may result via the "plastic lymph" which pours out from inflamed synovia.[278, 808] The characteristic deformities and optimal positions for joints were described.[278, 408] Practitioners should be more familiar with the indications for and technic of these nonsurgical orthopedic procedures; many of them do not require the services of orthopedists but can be done by practitioners and internists in the patient's own home.[278, 598] The uses of celluloid beds, leather-strip knee braces, leather-cork corsets, cock-up splints for wrists, caliper

splints for weak legs [234, 408, 480, 598] and also special measures for the care of arthritic feet were discussed. The last consist of rest and strapping, proper shoes, pads and bars, foot baths [56, 476] and a special foot rest for bedridden patients [296] which replaces the ordinary cradle and prevents weakening of feet which may lead to flattening of arches or "foot drop."

Indications and technic for manipulation without anesthesia were described. "The secret of manipulation without anesthesia is the quick short thrust" (Beauchamp). Underwater manipulation is an excellent follow-up to manipulations done with anesthesia.[808]

Surgical Orthopedic Measures: 1. Lactic Acid Injections and Miscellaneous Procedures. Waugh again [6, 799, 800] described the technic of this procedure which aims to stimulate natural local tissue reactions and evoke processes of repair in traumatized or infected joints. The solution is "prepared by combining lactic acid 0.2 per cent N/5 with procaine (novocaine) 2 per cent and 0.5 per cent NaCl" to make a sterile, approximately isotonic anesthetic with a pH of 5.6 to 5.8. Supplementing intra-articular injections were certain orthopedic measures (manipulation and splinting), but control joints for which injections were not used were but little improved. Fifty patients with inactive atrophic arthritis so treated obtained "at least 50 per cent recovery of function." In no case was inflammation clinically active.

Again discussed were the indications for and technic of arthrotomy and lavage with Dakin's solution,[278] arthrodesis,[278, 408, 702, 679] osteotomy (not very suitable in atrophic arthritis as it demands too long fixation) [278, 673] pseudarthrosis,[340, 673] excision of joints,[139, 278] arthroplasty [14, 139, 278, 408, 673] and special measures for deformed feet.[476] For an arthroplasty to be successful there must be sufficient healthy muscle to move the newly formed joint; since these are often absent in arthritics failure often results and joints may restiffen.[278, 673]

Synovectomy was done by some in chronic quiescent cases,[673, 794] by others [278, 585, 745] in active cases "predominantly synovial," without much bone change or capsular fibrosis. Capsulotomy was recommended for flexed knees; it may not increase the range of motion but will transfer that range of motion to a more useful part of the arc.[278, 673]

2. Manipulation under Anesthesia. The indications and technic of manipulation were reviewed.[57, 58, 234, 278, 476, 532, 533, 594, 808] Evipan or pentothal sodium were the anesthetics of choice. Results were good in knees, feet and ankles, poor in elbows, wrists, fingers and hips. Manipulation of shoulders is beneficial when restriction of motion involves the lower 60 degrees of the arc of abduction but not when it involves that from 60 to 120 degrees or all directions ("frozen shoulder").

Some advocated manipulation even in mildly active cases.[57, 234] It is often delayed too long; when done early for joints only slightly stiffened, it may save weeks of physical therapy by heat, massage, etc. Others approved manipulation only when active inflammation is entirely gone.[278, 532, 533] It should be approached with great caution and only be done by the skilled. Manipulation of joints which are notably destroyed is futile and dangerous. Most failures are due to overzealousness. Mennell cited the death of an arthritic patient 48 hours after a too vigorous manipulation. His advice was never to rely on an old roentgenogram, for osteoporosis occurs rapidly.

A series of manipulations is superior to one. A wise man does less than he might and does it more than once; a rash man takes a chance and goes out for full range. But he should remember that it is not his knee, the subsequent pain and reaction will not be his, nor will he suffer (save in reputation and possibly remorse) the pangs of disappointment when intense suffering reaps no reward. Mobility and pain are incompatible, hence any painful reaction must be transitory if one is to regain any degree of voluntary movement. If after 24 hours the patient cannot voluntarily move the joint without undue discomfort, through as wide a range as before manipulation, too much was attempted.

3. "Vitalium Mold-Arthroplasty." Arthroplasty has previously consisted in reshaping two joint surfaces and covering them with a lining that tended to prevent ankylosis, but blood clots within the joint after operation too often formed a fibrous tissue scar limiting motion. If the clot was confined to the capsular region and did not involve the interposed lining, less stiffness resulted. With this idea in mind Smith-Petersen (1925) developed the "two-stage mold arthroplasty" whereby an inert mold was inserted, around which nature could do its repair work. Early molds of glass, viscaloid and pyrex, were inadequate; bakelite was better, but vitalium was the best, and a new technic was developed with molds inserted into hips, and held in place by position only. When they were removed 21 to 25 months later, highly developed hyaline cartilage had covered the joint surfaces and the newly formed capsule consisted of dense fibrous tissue with a true synovial lining. Smith-Petersen has done this procedure in 29 cases since June, 1938 but it is too early for end results to be reported. He now thinks that the molds need not be removed.

Aware of Smith-Petersen's "unpublished work" with molds of various kinds, Hopkins and Zuck independently selected vitalium as a superior medium and performed an arthroplasty with such a cup February 11, 1938; the paper was published in July, 1938; at the time of a second report the results were "remarkable." Campbell [139] devised a vitalium cup for knee joints, but has used it in only four cases and has made no conclusions as yet.

[This work of Smith-Petersen is stimulating and most interesting. The method seems to promise results superior to older ones. We understand that results are best for ankylosed hips in which inflammation has ceased, and inferior (to date) in hips still the site of active atrophic arthritis.—Ed.]

4. Removal of Patella. This new procedure is advocated for arthritic knees affected by stiffness, pain and grating from osteophytic outgrowths due to various kinds of arthritis. Howell [408] reported "great benefit" therefrom in an unstated number of cases. The 11 patients operated on by Berkheiser included four with atrophic, three with hypertrophic, two with gonorrheal and two with traumatic arthritis. Thereafter there were less pain, more motion and a greater ability to maintain extension due to increased strength of the quadriceps. It is "not a specific treatment" for arthritis but a means of removing a mechanical impediment to function resulting from patellar exostosis.

[Results were not analyzed statistically.—Ed.]

Psychotherapy. Booth and Gordon [328] regarded psychotherapy as an important adjunct to other remedies. The patient's recovery and freedom from relapses depend largely on the degree of his emotional stability and on the satisfactoriness of his philosophy of life. "Chase out the 'jitterbug' and other bugs won't find it nearly so easy to thrive." [328] This can be done by altering his feelings of frustration through combined medicinal, physical and psychotherapy.

Prognosis: End Results. A third of Monroe's 267 clinic patients seen over a 10 year period did not return; of those treated for six months or more 40 per cent had "good results," 29 per cent had "fair improvement" and 30 per cent were "unimproved or worse." Those treated longest had the best results. Data on the life course of arthritis were again reported [2, 3, 563] by Nissen and Spencer: of 102 patients with "rheumatoid arthritis of unknown etiology" three took course A (one attack, practically full recovery), 44 took course B (remissions and relapses through life), 105 took course C (slow progressive crippling until death an average of 19 years later), nine took course D (rapid crippling and early death an average of seven years later).

Still's Disease

Little on Still's disease appeared. Atkinson published a historical and clinical review. Orthopedic measures for the deformed joints of arthritic children were reviewed.[679] A case of Still's disease in a girl aged seven years was reported [418] as unusual because amyloidosis, unsuspected during life, was found at necropsy.

[In our experience amyloidosis occurs frequently, rather than rarely, in Still's disease.—Ed.]

EDITORIAL

HUMORAL FACTORS IN THE CONTROL OF HYPERTENSION

THE demonstration by Goldblatt and his associates that injury to renal tissue produced by ischemia may result in sustained hypertension has stimulated a search for some substance to explain this activity. Some of the implications of Goldblatt's work have been discussed editorially in this journal.[1] It has been shown that the pressor response is not dependent upon the nervous system. The endocrine glands apparently play only a subsidiary part. Removal of the damaged kidney, however, abolishes the hypertension if the other kidney is normal. These facts led Goldblatt to suggest that the hypertension was excited by some substance that was formed in the damaged renal tissue.

The presence of pressor substances (renin) in extracts of renal tissue was first reported in 1898 by Tigerstedt and Bergmann.[2] This finding has since been corroborated by a number of investigators, although attempts to demonstrate an increased quantity of pressor substance in ischemic kidney tissue as compared with normal kidney have not been convincingly successful. The nature of the pressor substance (renin) in normal renal tissue has been studied extensively by Page and his associates.[3] On injection into normal animals renin causes a rise of blood pressure, and on perfusion through the rabbit's ear or through isolated organs it causes constriction of the vessels. On slow infusion into animals it causes a constriction of the renal vessels which, according to Corcoran and Page, is particularly marked in the efferent glomerular capillaries, thus resembling the condition which has been described in essential hypertension in man.

If, however, purified renin in Ringer's solution is perfused through a rabbit's ear, no vasoconstriction occurs. Renin requires for its activity some protein-like substance present in normal serum, which has been termed "renin-activator."[4] Renin is also probably a protein, it is thermolabile and in many other ways resembles an enzyme. Its action is slow in developing, it is affected by temperature, and the quantity or renin required for maximal effect is minute (1 to 30) as compared with that of "activator." The latter is probably the substrate.

The product of their interaction has been termed angiotonin. This has been isolated in relatively pure crystalline form by Page and Helmer[5] as an

[1] ANN. INT. MED., 1938, xii, *267–268.*

[2] TIGERSTEDT, R., and BERGMANN, P. G.: Niere und Kreislauf, Skand. Arch. Physiol., 1898, viii, 223–271.

[3] PAGE, I. H.: On the nature of the pressor action of renin, Jr. Exper. Med., 1939, lxx, 521–542.

[4] KOHLSTAEDT, K. G., HELMER, O. M., and PAGE, I. H.: Activation of renin by blood colloids, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 214–215.

[5] PAGE, I. H., and HELMER, O. M.: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator, Jr. Exper. Med., 1940, lxxi, 29–42.

oxalate and a picrate. It is a thermostable fluorescent substance soluble in water and alcohol and gives the color reaction for arginine but not those for the other aminoacids. On further incubation with renin it is gradually destroyed, and it is thought to be an intermediate product of the reaction between renin and renin-activator. A single injection into an animal causes a sharp rise in blood pressure, somewhat more prolonged than that produced by adrenalin, and a continuous infusion will maintain a high pressure for some time. It differs radically from adrenalin in other respects, however. The latter shows relatively little tendency to lose its effects after repeated injections. If, however, repeated injections of renin are administered to an animal, there is a progressive diminution of the responses obtained, and after about six doses the animal becomes refractory—a condition which Page et al. have termed "tachyphylaxis." They have shown that in part this state is owing to exhaustion of activator in the blood. Transfusions of blood from a normal animal, however, and even injections of a mixture of renin and renin-activator which is active in a normal animal, fail largely or completely to elicit a response in such a tachyphylactic animal. Renin added to blood from a tachyphylactic animal will not cause vasoconstriction when perfused through an isolated rabbit's ear. These facts suggest that renin injections stimulate the production or the liberation into the blood of some neutralizing antipressor substance.

There are a number of observations which indicate that the kidney may be the source of such a substance. Thus removal of the healthy kidney from a Goldblatt dog made hypertensive by partial obstruction of one renal artery greatly increases the hypertension. Bilateral nephrectomy (after the lapse of some hours) greatly increases the response to renin or angiotonin, both when injected into the animal and when added to the serum of such an animal and perfused through a rabbit's ear. Massive transfusions of normal blood abolish this hypersensitiveness, possibly by supplying the deficient inhibitor.

The extraction of such an inhibitor from kidney tissue was first reported by Grollman, Williams and Harrison.[6] They obtained in partially purified state a water soluble nonprotein substance, stable in dilute acid solution. This did not lower blood pressure in a normal animal but did so substantially in rats made hypertensive by partial nephrectomy, in Goldblatt dogs and in a few human cases. It was active by parenteral injection and also when administered by mouth. It reduced the response in normal animals to injections of renin. In animals with grave hypertension the fall in blood pressure might be accompanied by a severe reaction with prostration, anorexia, vomiting and uremia. The blood pressure gradually rose to its previous level a few days after the administration was stopped.

An extract containing a depressor substance probably identical with this

[6] GROLLMAN, A., WILLIAMS, J. R., and HARRISON, T. R.: The preparation of renal extracts capable of reducing the blood pressure of animals with experimental renal hypertension, Jr. Biol. Chem., 1940, cxxxiv, 115–121.

was independently obtained by Page et al.[7] by means of somewhat different procedures, both from normal kidney tissue and from muscle. It caused a drop in blood pressure when administered to dogs with hypertension produced by a cellophane perinephritis, as well as in hypertensive rats. The relief of associated symptoms in these animals is said to have been marked. In some cases extensive retinal lesions subsided and renal function improved. The effect gradually passed off after treatment was stopped, but it was usually maintained for from 4 to 40 days. Too precipitate lowering of the blood pressure, however, might result in uremia and fatal collapse.

They also report the administration of the extract to six cases of essential (benign) hypertension and to five cases of malignant hypertension in man. The blood pressure was lowered significantly in all, and symptoms were largely relieved. The effect was not maintained after treatment was stopped. Their results are somewhat confused by the fact that some of the extracts used were apparently not potent.

They point out that this substance differs essentially from other known depressants, particularly in the fact that its action is slowly elicited (12 to 48 hours), and that it is maintained for some days.

The significance of these observations is still uncertain and can be established only after much more study. It is not certain that the "hypothetical effect substance" of Goldblatt, presumably liberated from ischemic kidney tissue, is identical with the renin obtained from normal kidneys. Neither is it certain that either renin or the depressor substance is a normal secretory product of the kidney. Either might be simply degradation products of the kidney tissue. The evidence, however, does suggest the possibility that they may be antagonistic hormonal substances secreted by the kidney, and that under normal conditions the relative amounts liberated are so adjusted as to maintain the blood pressure within the usual limits. In the Goldblatt dog there appears to be an excessive formation of a pressor substance. In some other conditions the primary disturbance might be a deficient production of the depressor substance.

As to the therapeutic use of such products in hypertension in man, at best the results so far reported merely warrant further trial in hospitals under rigidly controlled conditions. In a disease as variable in its course as this, such experiments would have to be carried out on a large scale and over a period of several years before any definite conclusions could be drawn. The great importance of the subject, however, amply justifies the effort and expense which will be required to carry out such a study adequately.

P. C.

[7] PAGE, I. H., et al.: Reduction of arterial blood pressure of hypertensive patients and animals with extracts of kidneys, Jr. Exper. Med., 1941, lxxiii, 7–41.

REVIEWS

Fundamentals of Biochemistry. By T. R. PARSONS, B.Sc. (London), M.S. (Cantab.) Sidney Sussex College, Cambridge. Sixth edition. 461 pages; 13 × 19 cm. William Wood and Co., Baltimore. 1939. Price, $3.00.

This most recent edition of a volume which appeared originally in 1923 includes an entirely new chapter devoted to the sterols, their derivatives, and their function in the body mechanism.

In a book designed to fit the needs of a beginning student of physiology, the author has succeeded in keeping his subject matter intelligible to those who have had a minimum of previous knowledge in pure physics and chemistry. The author, in his foreword, alludes to what is undoubtedly the worst fault of the work—over-simplification of the physiological and chemical processes which govern the intricate mechanical device which is the human body.

Of necessity, a book, covering so broad a field in 424 pages, must be confined to the barest outline. Indeed the author believes that no single work can ever suffice for an intelligent understanding of the subject but must be supplemented by comparison with as many sources as possible. It is only after such pursuit that the student can "realize" his subject and become truly inspired by the combined intellectual attainments of scientists everywhere. Toward that purpose the author has concluded each chapter with comprehensive bibliographies for further investigation.

He opens his book with a discussion on the nature of living matter. This is followed by a résumé of the chemistry of the proteins, their properties and functions, metabolism, and the nitrogenous exchanges of the body as a whole. This section of the book is especially well organized and coördinated. Next in order he considers the fats and their relatives, the phospholipides and their place in human physiology. Following this is the chemistry of the carbohydrates, their metabolism, utilization, and pathology.

The remaining chapters are devoted to enzymes and oxidation catalysts, the vitamins, body pigments, the respiratory gases and gas tensions, and finally the functional importance of body fluids, both colloid and electrolyte.

For a broad, continuous version of the chemistry behind human physiology this volume should prove to be helpful to student and physician alike.

E. J. P.

Chemistry and Medicine. Edited by MAURICE B. VISSCHER, Professor of Physiology at the University of Minnesota. 296 pages; 15.5 × 23.5 cm. University of Minnesota Press, Minneapolis, Minn. 1940. Price, $4.50.

One of the most recently developed and most rapidly expanding aspects of medical science is that of chemistry. Because of the ever increasing interest in the field the committee which was planning for the celebration of the fiftieth anniversary of the founding of the University of Minnesota Medical School decided to limit the scientific program to the one theme: "Some Trends in Medical Progress with Particular Reference to Chemistry in Medicine." And it was because of the general excellence of the papers delivered before this assembly that this volume was published.

Under the editorship of Dr. Maurice B. Visscher the fourteen papers comprising the program were collected, edited, and published for the benefit of those who heard them delivered and the many others who will find these papers of interest.

Each of the papers delivered by men well known and highly regarded in their

respective fields is worthy of individual analysis, but the writer will confine himself to the general outlines of the topics. The book is divided into four sections, each section of which consists of three or four papers.

The first section is devoted to progress in the application of physical chemistry to medicine. Colloid chemistry and osmotic work in living systems is discussed by Dr. Herbert Freudlich and Dr. Maurice Visscher respectively. Such a discussion is necessarily highly technical but the speakers have assembled tables and charts to simplify and tabulate their subject matter. The final paper of the section is one delivered by Dr. John P. Peters on some reactions by which solutes may be differentially concentrated by the kidney.

The second section is one devoted to recent investigations in metabolism. It consists of reports of the studies made by Lee Irwin Smith in vitamin research and George O. Burr on the necessity of fats in the diet. Dr. Charles H. Best concludes the section with a review of the work being carried on at the University of Toronto with regard to heparin and thrombosis. He concludes his discussion with the results they have had with heparin used in various types of vascular surgery, in transfusions, and in cases of subacute bacterial endocarditis.

The third division of the book deals with immunity and chemotherapy. Dr. Michael Heidelberger recalls that it has been just 50 years since the relationship between pneumonia and the pneumococcus was discovered and how slowly but surely advances are being made in the field of immunology and serology. In his own words "It is apparent that new organic chemical techniques, powerful physico chemical tools, the application of vigorous quantitative micro methods of analytical chemistry, and the theories that have emerged from such methods have advanced our understanding of the chemical bases of immune processes to a considerable degree."

This quotation could be so aptly applied to a great number of fields especially that of the little known animal viruses upon which Robert G. Green spoke and that of the highly publicized and ever growing study of sulfanilamide and its derivatives and their mode of action upon which Dr. Perrin H. Long of Johns Hopkins University spoke.

The final section of the book is confined to the study of the nervous control of the organism and consists of talks by Drs. Irwine MacQuarrie, Herbert S. Gasser, Detlev W. Bronk, and Walter B. Cannon.

The volume is an interesting and valuable addition to any medical library and though the topics discussed are of a technical nature they are concisely and reasonably explained.

E. J. P.

Vitamin Therapy in General Practice. By EDGAR S. GORDON, M.D., M.A., and ELMER L. SEVRINGHAUS, M.D., F.A.C.P.; With a foreword by C. A. ELVEHJEM. 258 pages; 14.5 × 21 cm. The Year Book Publishers, Inc. Chicago, Illinois. 1940. Price, $2.75.

Here is very readable, concise and up-to-date information for physicians who need guidance to recognize the earlier manifestations of deficiency diseases and to prescribe effectively either with diets or preparations of vitamins. Advance in the nutrition field has been so rapid and the literature has become so voluminous, that few are able to keep abreast. This handbook is written by men who are well prepared for the task, and proper use of the information it contains will contribute importantly to the successful practice of medicine.

R. M. W.

Complete Guide for the Deafened. By A. F. NIEMOELLER, A.B., M.A., B.S.; With a foreword by HAROLD HAYS, M.D., F.A.C.S. 256 pages; 14 × 21 cm. Harvest House, New York. 1940. Price, $3.00.

It is not always considered wise that patients should know too much regarding their own ailments, but there are certain chronic incurable diseases attended by physical handicaps to which individuals so affected must adjust their lives, that they may be lived to the best advantage. Of such diseases, few, if any, are more common than those of the ear leading to hardness of hearing of greater or less degree. People who are deafened, near or below the average conversational level, are seriously hindered both from a social and occupational standpoint; but they are usually allowed to leave the office of the busy otologist, who has honestly told them there is nothing further he can do, without a word regarding certain adjustments that can be made or rehabilitation which may bring their lives nearer the normal. That they go away to become the victim of every charlatan with a new "cure" is not to be wondered at; that they accept each and every elaborate and expensive treatment with aroused hope is not surprising; and that finally they become introspective and skeptical, avoiding and rejecting all means of amelioration is only human. To meet this condition, Mr. A. F. Niemoeller has written the *Complete Guide for the Deafened,* and it would be a carping otologist, indeed, who would hesitate to place this book in the hands of any hard of hearing patient.

The author has particularly stressed the necessity of careful ear examinations and treatments by competent otologists. The authorities he has quoted are among the most outstanding American aurists of recognized scientific and clinical ability. New or experimental treatments are mentioned only if sponsored by recognized investigators, and any controversial factors are freely admitted. Recognition of deafness in children and its prevention is emphasized. The value of hearing-aids both individual and group, with their proper use is well handled. Lip-reading and its limitation is described. As a matter of fact, there are few if any phases of ear diseases, and the deafness resulting therefrom that are not adequately touched upon in the 77 very short chapters into which the author has divided his book.

The style is simple, accurate, and most readable. One might feel that some of the chapter headings are a bit sensational as compared to the conservative contents of the text itself, but this is only mentioned as a constructive criticism of form.

The book is profitable reading for all otologists who wish to keep abreast of the social aspects of deafness. It should be in the library of all Leagues for the Hard of Hearing, and it may be safely recommended to all deafened people, who are anxious to reconstruct their lives to meet their handicap.

J. W. D.

Military Preventive Medicine. By GEORGE C. DUNHAM, M.A., M.D., Dr. P. H., etc.; Lieutenant Colonel, M.C., U.S.A.; Director, Department of Preventive Medicine, Army Medical School. 3rd. edition. 1198 pages; 16 × 23.5 cm. The Book Service, American Public Health Association, 50 West 50th Street, New York. N. Y. Price, $2.50.

Colonel Dunham presents well the principles of Army epidemiology and sanitation. The many illustrations make the subject matter of the text readily understood. This volume should be invaluable to the many physicians now entering the Army Medical Corps.

W. S. L., JR.

COLLEGE NEWS NOTES

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1941–42, are herewith announced and published:

President-Elect ..... James E. Paullin, Atlanta, Ga.
First Vice President ..... D. Sclater Lewis, Montreal, Canada.
Second Vice President ..... Thomas F. Holt, Wichita, Kan.
Third Vice President ..... Samuel E. Munson, Springfield, Ill.

The election of nominees shall be by the members of the College at its Annual Business Meeting, Boston, Mass., April 24, 1941. These nominations do not preclude nominations made from the floor at the Annual Meeting itself. Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,

Reginald Fitz, Boston, Mass.,
Fred M. Smith, Iowa City, Iowa,
Charles F. Tenney, New York City,
Ernest B. Bradley, Lexington, Ky.,
David P. Barr, *Chairman*, St. Louis, Mo.
Committee on Nominations

Splendid Course in Military Medicine Offered Members of the American College of Physicians

Through the collaboration of the Army Medical Corps, the Navy Medical Corps and the United States Public Health Service, an unusual postgraduate course in Military Medicine has been arranged for members of the College who are interested. This course will be given in Washington, D. C., from April 7 to April 19.

Many subjects will be presented by outstanding experts from military, naval and civil life. Although stress will be placed upon the relationship of professional activities to the Preparedness Program and to possible war, the subjects will be of a strictly medical nature. Venereal diseases, tropical medicine and infectious diseases will be considered in great detail, as well as many other subjects that should be of considerable interest to internists and physicians in general. Washington is now overflowing with medical talent, and this has been commandeered for the course. Furthermore, experts from afar are being invited to participate. Members attending this course will have an opportunity to observe at first hand the outstanding medical institutions of the National Capital. Whether they are interested in participation in the Preparedness Program or not, they should receive a great deal of helpful information.

One of the most pleasant times of the year to visit Washington is April. The weather is usually excellent, and the city is beginning to take on its Spring beauty. Although the course will consume the greater part of the time, there will undoubtedly be ample opportunity for sight-seeing.

This course is a new venture for the American College of Physicians, and it is hoped that a sufficient number of Fellows and Associates will sign up for it to make it worth while for the instructors to exert their best efforts.

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Tomás Cajigas, Washington, D. C.
Dr. Gustave William Dishong, Omaha, Nebr.
Dr. Harrison Fitzgerald Flippin, Philadelphia, Pa.
Dr. Emmet F. Horine, Louisville, Ky.
Dr. Ontie Hovenden, McGill, Nev.
Dr. Alexander B. Leeds, Chickasha, Okla.
Dr. Jesse M. W. Scott, Schenectady, N. Y.
Dr. Jacob Segal, New York, N. Y.
Dr. Thomas H. A. Stites, Cresson, Pa.
Dr. Warren Thompson, Omaha, Nebr.
Dr. John Walter Torbett, Sr., Marlin, Tex.
Dr. Louis A. Van Kleeck, Manhasset, N. Y.
Dr. I. Ogden Woodruff, New York, N. Y.

Gifts to the College Library

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Books

Dr. William S. Hoffman, F.A.C.P., Chicago, Ill.—"Photelometric Clinical Chemistry";
Dr. Maurice Lewison, F.A.C.P., Chicago, Ill.—"Manual of Physical Diagnosis";
Dr. John Walter Torbett, Sr., F.A.C.P., Marlin, Tex.—"Practical Poems for Daily Use";
Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Electrocardiography in Practice."

Reprints

Dr. H. Sheridan Baketel, F.A.C.P., Jersey City, N. J.—1 reprint;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—2 reprints;
Lt. Col. J. R. Darnall, F.A.C.P., (MC), U. S. Army—2 reprints;
Dr. Eugene H. Drake, F.A.C.P., Portland, Maine—2 reprints;
Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Joseph F. Elward (Associate), Washington, D. C.—1 reprint;
Dr. Jason Engels Farber (Associate), Buffalo, N. Y.—1 reprint;
Dr. Lynn T. Hall, F.A.C.P., Omaha, Neb.—1 reprint;
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Edward Kupka, F.A.C.P., Olive View, Calif.—6 reprints;
Dr. Perry Scott MacNeal (Associate), Philadelphia, Pa.—1 reprint;
Dr. Harold R. Merwarth, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Curtis T. Prout, F.A.C.P., Arlington Heights, Mass.—1 reprint;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—23 reprints;
Dr. Martin Van Buren Teem, F.A.C.P., Marietta, Ga.—1 reprint;
Dr. Harry B. Thomas (Associate), York, Pa.—1 reprint;
Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif.—1 report.

1941 John Phillips Memorial Award

On the recommendation of the Committee on Fellowships and Awards, the Board of Regents of the American College of Physicians, by unanimous resolution, has voted that the John Phillips Memorial Medal for 1941 be awarded to Dr. William Christopher Stadie, Associate Professor of Research Medicine at the University of Pennsylvania, Philadelphia, for his significant contributions to the knowledge of anoxia, cyanosis and the physical chemistry of hemoglobin, and more especially for his recent studies on the subject of fat metabolism in diabetes mellitus.

Oklahoma Members Hold Regional Meeting

The members of the American College of Physicians in Oklahoma held their annual meeting, February 22, 1941, in Oklahoma City, under the Governorship of Dr. Lea A. Riely, F.A.C.P. There were clinics and round table discussions during the day and a dinner and social meeting in the evening.

In addition to the annual meeting on February 22, the College members in Oklahoma, in conjunction with the Oklahoma Internists Association, each year furnish one day's program at the meeting of the Oklahoma State Medical Association. This group also has a "get together" meeting at the Annual Fall Clinical Conference of the Oklahoma City Clinical Society.

Dr. Everett C. Fox, F.A.C.P., Dallas, Tex., was elected a member of the Board of Directors of the American Academy of Dermatology and Syphilology for a three-year term at the annual session of this society in Chicago, December 8–10, 1940.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., has been chosen as the first recipient of the John Jeffries Award. This award was presented to Dr. Bauer at the Honors Night Dinner of the Institute of the Aeronautical Sciences on January 28, 1941. The John Jeffries Award, which is given for contributions to aviation medicine, was established in honor of the first American to make scientific observations from the air. The Institute will present the John Jeffries Award annually for outstanding contributions to the advancement of aeronautics through medical research.

Dr. Bauer, the recipient for 1940, was the first Medical Director of the Aeronautics Branch of the Department of Commerce. He organized and was the first President of the Aero Medical Association and is now Editor-in-Chief of its official publication, the Journal of Aviation Medicine. He is consultant in aviation medicine and cardiology to the Civil Aeronautics Authority.

Dr. James B. Bullitt, F.A.C.P., Chapel Hill, was elected President of the North Carolina Pathological Society at its recent annual meeting in Charlotte, and Dr. C. C. Carpenter, F.A.C.P., Wake Forest, was reëlected Secretary and Treasurer of the Society.

Dr. William Gerry Morgan, M.A.C.P., Washington, D. C., was elected Chairman of the newly formed Washington branch of the American Bureau of Medical Aid for China at a meeting held recently at the Chinese Embassy in Washington.

On March 14, 1941, Dr. Harold J. Harris (Associate), Westport, N. Y., will give a radio address on the subject of "The Relationship of Brucellosis (Undulant Fever) to Tuberculosis" over station WNYC, under the auspices of the New York Tuberculosis and Health Association.

The Executive Board of the American Public Health Association has announced that this Association will hold its 70th Annual Meeting in Atlantic City, N. J., October 14–17, 1941.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "The Newer Nutrition and Its Application to Clinical Medicine" to the Staff of the Cooper Hospital in Camden, N. J., on December 13, 1940.

Dr. John F. Kenney, F.A.C.P., Pawtucket, R. I., spoke on "Electrocardiography" at the monthly meeting of the Pawtucket Medical Association, December 19, 1940.

On January 8, 1941, Dr. Kenney took part in a symposium on "The Medical Management of Pre-Operative Phases of Biliary Tract Disease" at the combined meeting of the Worcester City Hospital Staff and the Worcester District Medical Society.

Dr. J. Arthur Buchanan, F.A.C.P., Brooklyn, N. Y., has been named Director of Medicine at the Wyckoff Heights Hospital by its Board of Trustees, with authority to reorganize the medical service at that hospital.

The New Jersey Gastro-Enterological Society held a symposium on "Lesions of the Stomach, Duodenum and Jejunum" at the Academy of Medicine, Newark, N. J., February 3, 1941. Dr. Hyman I. Goldstein (Associate), Camden, N. J., presided at this meeting. Among others who participated were: Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.; Dr. Charles L. Brown, F.A.C.P., Philadelphia, Pa.; Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J.; Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.; and Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.

The Third Annual Forum on Allergy was held in Indianapolis, Ind., January 11–12, 1941. Dr. Bela Schick, New York, N. Y., was presented with a gold medal for his pioneer work with von Perquit on allergy. Among those taking part in the program were: Dr. George Waldbott, F.A.C.P., Detroit, Mich.; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio; Dr. Oscar Swineford, Jr., F.A.C.P., University, Va.; Dr. Theodore Squier, F.A.C.P., Milwaukee, Wis.; Dr. John M. Sheldon (Associate), Ann Arbor, Mich.; Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.; Dr. Carl D. Figley, F.A.C.P., Toledo, Ohio; Dr. J. Warrick Thomas, F.A.C.P., Cleveland, Ohio; Dr. Homer E. Prince, F.A.C.P., Houston, Tex.; Dr. Carl Way (Associate), Akron, Ohio; Dr. Frank A. Simon, F.A.C.P., Louisville, Ky.; and Dr. C. B. Bohner, F.A.C.P., Indianapolis, Ind., who was a member of the local committee on arrangements.

Dr. Maurice J. Dattelbaum, F.A.C.P., Brooklyn, N. Y., President of the Medical Society of the County of Kings, was honored at a dinner given by his friends on January 28, 1941.

On January 24, 1941, Dr. William H. Lohman, F.A.C.P., Brooklyn, N. Y., conducted the Scientific Session at the 29th meeting of the Brooklyn Society of Internal Medicine.

Dr. H. Beckett Lang, F.A.C.P., Albany, N. Y., has been appointed Superintendent of the Buffalo State Hospital. He was also recently appointed Lecturer in Social Psychiatry at the Millard Fillmore School of Social Work, University of Buffalo, and Lecturer in Psychiatry at the University of Buffalo Medical School.

Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill., spoke before the Schuyler and Cass County physicians at the Beardstown (Ill.) Hospital on January 8, 1941, on "Influenza and Respiratory Diseases" at the request of the Educational Committee of the Illinois State Medical Society.

Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., was the guest speaker at a recent meeting of the Wisconsin Anti-Tuberculosis Association held in Madison, Wis. Dr. Amberson spoke on "Diagnosis of Pulmonary Tuberculosis" and "Principles of Treatment of Tuberculosis."

Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., recently addressed the Polk County Medical Society at Webster, Wis., on "Vitamin K in Cases of Liver Depletion with and without Jaundice."

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., delivered the eighth E. Starr Judd Lecture at the University of Minnesota, January 15, 1941. His subject was "The Mechanisms of Gastric Secretion."

Dr. Edgar Mayer, F.A.C.P., New York, N. Y., spoke on "Tuberculosis in the Army under Present Epidemiologic Conditions" at the meeting of the New York State Chapter of the American College of Chest Physicians, January 17, 1941.

Dr. William J. Kerr, F.A.C.P., San Francisco, Calif., Professor of Medicine at the University of California Medical School, has been elected an honorary member of the Liga Argentina contra el Reumatismo, Buenos Aires.

Among those who conducted seminars at the Delaware State Hospital, Farnhurst, Del., November 24–26, and December 2–5, 1940, were:

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., "Psychiatry";
Dr. Charles W. Dunn, F.A.C.P., Philadelphia, Pa., "Endocrinology."

The Wisconsin State Board of Health and The Industrial Nurses of Wisconsin sponsored a symposium on "Industrial Public Health Nursing Services" in Milwaukee, Wis., February 20–22, 1941. Dr. William S. Middleton, F.A.C.P., Madison, Wis., presided at one of the sessions and Dr. Norbert Enzer, F.A.C.P., Milwaukee, spoke on the "Relationship of Cardio-Vascular Diseases to Accidents." Dr. Elston L. Belknap, F.A.C.P., Milwaukee, conducted a tour of inspection of several industrial plants.

Dr. John Walter Torbett, Sr., F.A.C.P., Marlin, Tex., has written in addition to his scientific articles, several books of poems of which his latest, "Practical Poems for Daily Use," has just been presented to the College Library of Publications by Members. This volume is a successor to "Joytown Jingles," "Pastime Poems," and "Centennial Songs." The present volume has been published by the Methodist Orphans' Home at Waco, Tex. The poems are devoted to the homely virtues of faith, hope, cheer, happiness and friendship, so representative of the author.

ERRATUM: *Page 1139, January 1941* ANNALS, *Table I, figures given as "No. of Cases 36, Mortality 60%" should read "No. of Cases 26, Mortality 84.6%."*

OBITUARIES

DR. ROGER BROOKE

Dr. Roger Brooke, F.A.C.P., Brigadier General, U. S. Army, died at the Walter Reed General Hospital in Washington on December 18, 1940, of a heart ailment. He was born at Sandy Spring, Maryland, on June 14, 1878, the son of Roger and Louisa (Thomas) Brooke. After graduating from the George School at Newton, Pa., he entered the medical school of the University of Maryland, in Baltimore, where he graduated in 1900. He joined the medical corps of the Army on June 29, 1901, as a first lieutenant, passed through the various grades and was appointed a brigadier general on January 29, 1938. After graduating from the Army Medical School in the class of 1902 he had a tour of duty in the Philippines. Other early service included duty at Fort Bayard, N. M., at the Letterman General Hospital in San Francisco, at Fort Leavenworth, Kansas, and as attending surgeon in Washington. He spent the period of the World War in instruction work, serving from September 1917 to December 1918, first as senior instructor and later as commanding officer of the Medical Officers Training Camp at Camp Greenleaf, Georgia, where 10,000 officers and 70,000 enlisted men were prepared for service with the armed forces. For this service he was awarded the Distinguished Service Medal.

Later tours of duty included the office of The Surgeon General where he was chief of the tuberculosis section, division of medicine; the Veterans' Bureau, as chief medical consultant; at Gorgas Hospital in the Canal Zone, and at Fort Sam Houston, Texas, where he was commanding officer of the large station hospital. Brought again to the office of The Surgeon General in 1935 he was placed in charge of the professional service division. While on this duty he was promoted to brigadier general and sent to the command of Letterman General Hospital. He was later transferred to the post of commandant of the Medical Field Service School at Carlisle Barracks, Pa., his station at the time of his death.

Early in his army career, General Brooke interested himself in internal medicine and became well recognized as one of the foremost in that field that the corps has produced. Well versed in the study of tuberculosis from his early service at Fort Bayard, he instituted the overseas recruit depot at Fort Slocum, N. Y. in 1935, the first routine examination of the chest by roentgen-ray in the military service. He was a Fellow of the American College of Surgeons, and of the American College of Physicians, a member of the American Medical Association, the American Society of Tropical Medicine, the National Tuberculosis Association, and the Association of Military Surgeons of the United States. He contributed a number of articles to the pages of the *Military Surgeon* and to other medical journals.

General Brooke was married in 1905, at Baltimore, to Grace M. Macomb of that city, who, with a son, Roger, of San Francisco, survives him.

In the death of General Brooke the medical corps loses one of its exceptional students of medicine, one whose interest in the advances of his profession never flagged from the day of his graduation. He had a gift of vision of the possibilities of disease prevention. He was quiet spoken, gentle in manner, modest and unassuming in the exercise of his great talents. He leaves a host of devoted friends who will long remember him for his notable qualities and for the simple strength of his character.

The funeral services were held on December 20, 1940, at the Fort Myer Chapel, the Rev. Ivan L. Bennett, Chaplain, U. S. Army, officiating. Burial was in Arlington Cemetery.

JAMES M. PHALEN,
Colonel, U. S. Army (Retired).

DR. EDGAR A. HINES

In the death of Edgar Alphonso Hines, F.A.C.P., of Seneca, S. C., on Nov. 27, 1940, South Carolina lost a faithful, competent and indefatigable servant and organized medicine a devoted adherent.

Dr. Hines was born at Goldsboro, N. C., November 19, 1867. He attended Clemson College (S. C.) as a special student in chemistry and received his M.D. degree from the Medical College of the State of South Carolina in 1891. Dr. Hines served on the staff of Oconee County Hospital; was a member of the faculty of Southern Pediatric Seminar, and served one year as extramural lecturer on pediatrics at the Medical College of the State of South Carolina. He was vice chairman of the State Board of Health and one of the founders of the Board's bureau of child hygiene. During 1915 he was superintendent of the Anderson County Hospital. He was secretary of the South Carolina Medical Association and editor-in-chief of the *Journal of the South Carolina Medical Association* for many years. Dr. Hines was a Fellow of the American Medical Association and a member of the House of Delegates of this Association from 1910 to 1928 and from 1930 to 1940, and a Fellow of the American College of Physicians since 1924. He was a member and past president of the South Carolina Pediatric Society and the Piedmont Postgraduate Clinical Assembly; member of the American Academy of Pediatrics and diplomate of the American Board of Pediatrics; a member of the International Congress of School Hygiene and in 1913, session chairman of the Congress in Buffalo. He was also a member of the Oconee County Medical Society, South Carolina Medical Association, South Carolina Pediatric Society, South Carolina Hospital Association, Southern Medical Association, American Public Health Association and American Medical Editor's Association. He was Chairman of the Committee on Medical Preparedness for South Carolina.

Dr. Hines never ceased to be a student and inquirer and to the moment

of his sudden death was enthusiastically interested in furthering the best in medicine. With all, a kindly, unassuming man of many friends and attachments, his passing leaves a vacancy not easily or soon to be filled.

KENNETH M. LYNCH, M.D., F.A.C.P.,
Governor for South Carolina

DR. ROBERT TORREY

Dr. Robert G. Torrey, F.A.C.P., former President of the Medical Board of the Philadelphia General Hospital, died at his home at 1716 Locust Street, Philadelphia, on January 11, 1941.

Dr. Torrey was born in Richmond, Virginia, July 12, 1873, and received his M.D. degree from the University of Pennsylvania School of Medicine in 1906.

He had been Visiting Physician at the Philadelphia General Hospital since 1916, and for many years was Physician at the Medical Dispensary of the University Hospital, Physician at the Pennsylvania State Tuberculosis Dispensary, and Visiting Physician at St. Mary's Hospital.

Since 1916 Dr. Torrey had been Associate in Medicine at the University of Pennsylvania School of Medicine, and since 1931, Professor of Medicine at the Woman's Medical College of Pennsylvania.

He was elected to Fellowship in The American College of Physicians in 1923; was a member of The Philadelphia County Medical Society; the American Medical Association; the American Rheumatism Association, the American Heart Association; and the Racquet Club.

Dr. Torrey is survived by his wife, Mrs. Florence Smith Torrey; two sons, Robert D. and Philip C. Torrey; three brothers, Donald F., James E., and Arthur M. Torrey, and a sister, Miss Gertrude Torrey.

In addition to his high standing in the medical profession, particularly among his colleagues on hospital staffs and at the Woman's Medical College, Dr. Torrey had a large circle of close friends. His passing is a great loss to the profession of Philadelphia, his family and his intimates.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. HARRY E. WELCH

Dr. Harry E. Welch, a Fellow of the American College of Physicians since 1921, died in Youngstown, Ohio, on August 12, 1940, at 79 years of age.

Dr. Welch was born near the Mahoning River "by the light of the Falcon furnace"—Youngstown, a town of only 4,000 persons at that time. He was graduated from Rayen School there and during vacation periods and after school he filled-in as a steel worker.

In October of 1882 he matriculated at Western Reserve University, and

in 1886 after being graduated from the Western Reserve University School of Medicine he enjoyed a rare privilege for students of those days—he went abroad to study in Vienna, London and Berlin. Special attention was given to microscopy and pathology.

In 1887 he began the practice of medicine in Youngstown and in 1891 became Coroner of that city. A year later he was appointed Health Officer. His work in that capacity was so efficient that many times the City of Youngstown was especially designated as a healthful city.

For many years Dr. Welch conducted a medical service at the Youngstown Hospital and also served as a member of the Board of Trustees of this hospital. He served as local physician for the Erie Railroad for a period of forty years. He was a firm believer in organized medicine and maintained his affiliation with the American Public Health Association.

Dr. Welch had a keen appreciation for clinical medicine and his Sunday morning discussions in the staff room at the hospital were enjoyed by many of his professional friends for years. His great effort in establishing an outstanding sanitary community in Youngstown will always be remembered, not only by the medical profession but also by the laity.

He was unassuming in character, staunch in his belief of principle and genuine in his love for the public welfare. His passing leaves a void difficult to fill but a reputation we all could well emulate.

A. B. Brower, M.D., F.A.C.P.,
Governor for Ohio

DR. ROLAND BEATTY TUPPER

Dr. Roland Beatty Tupper was born in Fresno, Calif., on July 26, 1886, and was graduated from Cooper Medical College in 1910. He served as intern at St. Luke's Hospital of San Francisco and later was a member of the staff of that institution. While a resident of San Francisco, he served as Assistant Clinical Professor of Medicine at Stanford University School of Medicine. During the World War he was a member of the Stanford Group in Scotland at the U. S. Naval Base Hospital.

Soon after the World War Dr. Tupper located in Fresno, where he was Chief of the Men's Medical Service at the General Hospital of Fresno County, which position he held until the time of his death. He was also a member of the staff of the Burnett Sanitarium. He was a Fellow of the American Medical Association, a member of the American College of Chest Physicians and an Associate of the American College of Physicians.

Dr. Tupper was held in high esteem as a consultant, as well as a practitioner of internal medicine, and his death on October 30, 1940, was a distinct loss to the profession and to his community.

W. E. R. Schottstaedt, M.D., F.A.C.P.,
Fresno, California

PROGRAM

TWENTY-FIFTH ANNUAL SESSION

AMERICAN COLLEGE OF PHYSICIANS

BOSTON, MASS.

April 21–25, 1941

GENERAL SESSIONS AND LECTURES

James D. Bruce, President

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Earle M. Chapman
Reginald Fitz
Dwight O'Hara
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Elliott P. Joslin.....New England Deaconess Hospital
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James H. Means.....Massachusetts General Hospital
Cadis Phipps.....Boston City Hospital
Joseph H. Pratt.....Boston Dispensary
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Mrs. James H. Means
Mrs. George R. Minot
Mrs. B. Harrison Ragle
Mrs. Fritz B. Talbot
Mrs. James H. Townsend
Mrs. Thomas V. Urmy
Mrs. Soma Weiss

Mrs. Conrad Wesselhoeft

HONORARY COÖPERATING COMMITTEE

C. Sidney Burwell, Dean, Harvard Medical School
A. Warren Stearns, Dean, Tufts College Medical School
Bennett F. Avery, Dean, Boston University School of Medicine
Walter G. Phippen, President, Massachusetts Medical Society
David Cheever, President, Boston Medical Library
Albert A. Hornor, President, Suffolk District Medical Society
Frank H. Lahey, President-Elect, American Medical Association
John J. Reddy, Colonel, Medical Corps, U. S. Army, First Corps Area Army Base
John L. Neilson, Captain, Medical Corps, U. S. Navy, First Naval District, Navy Yard

Paul J. Jakmauh, State Commissioner of Public Health
Clifton T. Perkins, State Commissioner of Mental Health
G. Lynde Gately, Commissioner of Public Health for Boston
Grover A. Kempf, Medical Officer in Charge, U. S. Marine Hospital

NEW ENGLAND GOVERNORS FOR THE AMERICAN COLLEGE OF PHYSICIANS

Eugene H. Drake.....Maine
Robert B. Kerr.....New Hampshire
Paul K. French.....Vermont
Alexander M. Burgess.....Rhode Island
Charles H. Turkington.....Connecticut

GENERAL INFORMATION

Boston Headquarters

Hotel Statler, Park Square at Arlington Street

Hotel Statler will be headquarters for Officers, Regents, Governors and members of the College, as well as general headquarters for registration, technical exhibits, general scientific sessions, special lectures and panel discussions.

The Copley Plaza Hotel, three blocks removed from Hotel Statler, has graciously made available to the College one of its public halls in which one series of panel discussions will be conducted daily.

List of Boston Hotels	Blocks from Hotel Statler	Rates per day, with private bath	
		Single Room	Double Room
HOTEL STATLER		$3.50–8.00	$5.00–12.00
HOTEL COPLEY PLAZA	3	4.00–6.00	6.00–12.00
Bradford Hotel	3½	3.00–4.00	4.50– 6.00
*Copley Square Hotel	4	3.00–3.50	5.00– 6.00
Kenmore Hotel	14	3.50–5.00	5.00– 7.00
*Lenox Hotel	4	2.75–3.50	3.50– 6.00
Lincolnshire Hotel	7	3.00–4.00	5.00– 7.00
Myles Standish	14	3.00–3.50	4.00– 5.00
Puritan Hotel	11	4.00–5.00	5.00– 7.00
Ritz-Carlton Hotel	2½	5.00–8.00	8.00–10.00
Sheraton Hotel	15	3.00–3.50	4.00– 6.00
Somerset Hotel	12	3.50–4.00	6.00– 7.00
*Touraine Hotel	3	3.50–5.50	5.00– 7.50
Victoria Hotel	4	2.50–4.00	4.00– 6.00
Westminster Hotel	2	2.50–3.00	4.00– 5.00

* Rooms without bath also are available at lower rates than quoted.

Rates for suites and for large rooms accommodating three or four persons furnished upon application.

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates quoted are, in some instances, only for this occasion.

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1941 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Medical students (fourth year only) pursuing courses at any approved medical school in Massachusetts (Harvard Medical School, Boston University School of Medicine, Tufts College Medical School), without registration fee, upon presentation of matriculation cards, or other evidence of

registration at these institutions; exhibits, morning lectures, general sessions.

(*d*) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, panel discussions and general sessions.

(*e*) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(*f*) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open on the mezzanine floor of the Hotel Statler on Sunday, April 20, from 2:30 to 5:00 in the afternoon, and from 7:00 to 9:00 in the evening. Thereafter the Registration Bureau will be open daily, 8:30 a.m. to 6:00 p.m., Monday to Friday, April 21–25.

REGISTRATION BLANKS FOR ALL CLINICS AND PANEL DISCUSSIONS will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session. Advance reservations for clinics and panels can be made for members only.

BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Hotel Statler.

TRANSPORTATION—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Physicians should consult their local ticket agents.

Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting. A map will be published in the formal program on which will be clearly indicated the headquarters, and the clinics and medical schools at which morning clinics and demonstrations will be held. Transportation to these points will be offered in three forms:

(1) A general bus transportation ticket on sale at the Registration Bureau, which will entitle the holder to bus transportation each morning throughout the week at 8:45 a.m. (Columbus Street exit of the Hotel Statler, or the Huntington Avenue entrance of the Hotel Copley Plaza) to go to any clinic or demonstration point and return from that same point at 12:00 m.

(2) Taxicabs—The Checker Taxicab Company and the Town Taxicab Company have guaranteed the following rates:

From Hotel Statler to:	Taxis	
	Checker	Town
Copley Plaza	$ .25	$ .30
Back Bay Station	.30	.35
Trinity Place Station	.30	.30
South Station	.45	.45
North Station	.65	.55
Massachusetts Memorial Hospital	.50	.50
City Hospital	.55	.50
Peter Bent Brigham Hospital	.75	.65
Good Samaritan Hospital	.70	.70
Children's Hospital	.70	.65
Beth Israel Hospital	.70	.65
Psychopathic Hospital	.75	.75
N. E. Deaconess Hospital	.80	.75
Haynes Memorial Hospital	1.30	1.30
Massachusetts General Hospital	.50	.50
Joseph Pratt Diagnostic Hospital	.40	.40

(3) Subway—The subway entrance is just a few yards in front of the Hotel Statler entrance. Subway trains reach all points.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5:00 p.m., Thursday, April 24, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, and the annual reports of the Secretary-General, Executive Secretary and Treasurer will be presented. The President-Elect, Dr. Roger I. Lee, Boston, Mass., will be inducted into office.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled, as indicated. Special meetings will be announced and posted.

A *dinner meeting* of the Board of Regents and of the Board of Governors will be held at the Hotel Statler, Parlor A, mezzanine floor, Sunday evening, April 20, at seven o'clock.

COMMITTEE ON CREDENTIALS

Sunday, April 20, 9:00 a.m.....Hancock Room, mezzanine floor, Hotel Statler

BOARD OF REGENTS

Hancock Room, mezzanine floor, Hotel Statler

Sunday, April 20, 2:30 p.m.
Tuesday, April 22, 12:00 m.*
Friday, April 25, 12:00 m.*

BOARD OF GOVERNORS

Hancock Room, mezzanine floor, Hotel Statler

Monday, April 21, 5:00 p.m.
Wednesday, April 23, 12:00 m.*

SPECIAL FEATURES

MONDAY, APRIL 21, 1941

THE ANNUAL SMOKER—Directly following the last presentation of the second General Session on Monday evening in the same hall (Statler Ballroom), the so-called Smoker will be held. Though plenty of tobacco will be available, the emphasis this year will be placed on food, fun, friendship, beer and music. There will be no formal vaudeville or floor show, but ample opportunity will be provided for renewing old acquaintances and establishing new ones. Oyster bars will be prominent, and for those allergic to seafoods, a collation of orthodox items for satisfaction of the inner man will be available. A small mobile orchestra (Ruby Newman's) will provide appropriate informal music to accompany such barber shop tendencies as may crop up, but there will be no organized community singing. Perhaps a few short moving picture presentations will be offered—nothing, however, which is likely to tax the intellect.

In short, Monday will provide a modified free evening. Your Committee believes that the Monday evening gathering can be set up to further the social aspects of the College without detracting from the entertainment value of the Annual Smoker.

Fellows and Associates, local and visiting physicians and the technical exhibitors are invited to attend the Smoker as guests of the College. The registration badge is all that will be needed for identification.

* Buffet luncheon served.

TUESDAY, APRIL 22, 1941

SYMPHONY CONCERT—8:45 p.m., Symphony Hall, corner Massachusetts Avenue and Huntington Avenue—Largely through the good offices of Dr. Roger I. Lee, our President-Elect, Dr. Serge Koussevitzky, Conductor of the Boston Symphony Orchestra, has invited the members of the College and their guests to Symphony Hall on Tuesday evening.

Your Committee knows that this nationally famous orchestra and its conductor need no introduction to the members of the College—and that they will consider this invitation in the light of a great honor. The only way in which we can show our appreciation is to see that there is a full house on that night, which should not be difficult under the circumstances.

It is suggested that those members who are planning dinner parties schedule them for Tuesday evening at 6:30, so that ample time will be available for comfortable dining before the doors of Symphony Hall close at nine o'clock.

Though the actual musical program has not been arranged, our experience with Dr. Koussevitzky as a program maker makes us confident that, as far as entertainment goes, the concert will be the high-light of the meeting.

All connected with the College meeting, members, guests, exhibitors and friends, are included in this invitation. They may bring local friends—in fact, they are urged to do so. Tickets will be distributed at the Hotel Statler on Monday and Tuesday. Opportunity to reserve seats ahead of time will be afforded members at the time of distribution of the final Program in February.

WEDNESDAY, APRIL 23, 1941

CONVOCATION OF THE COLLEGE—8:30 p.m., Ballroom, Hotel Statler. All members of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in Parlor "A" on the mezzanine floor at 7:45 o'clock, preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation promptly at 8:30. It is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation ceremony will include the President's Address and the Convocational Address which this year will be delivered by Dr. James Alex. Miller, F.A.C.P., Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons; former President of the American College of Physicians and former President of the New York Academy of Medicine. The award of the John Phillips Memorial Medal will be made to Dr. William C. Stadie, of Philadelphia, and the recipients of the Research Fellowships of the College for 1941 will be announced. The newly elected Fellows will be presented by the Secretary-General and, after subscribing to the Fellowship Pledge, will be inducted by the President.

The President's Reception and Dance will follow immediately after the Convocation, and will be held in the Ballroom of the Hotel Statler. At the end of the Convocation exercises, the audience is requested to leave the Ballroom for approximately twenty minutes while the Hall is rearranged for the Reception and Dance. All members and their guests are requested to pass along the receiving line. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Music for the Reception and Dance will be furnished by Ruby Newman and his orchestra.

THURSDAY, APRIL 24, 1941

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Ballroom of the Hotel Statler at eight o'clock. Dr. William B. Breed, General Chairman of the Twenty-fifth Annual Session of the College, will be the Toastmaster. The address of the evening will be delivered by Earnest Albert Hooton, Ph.D., B.Litt., Sc.D., Professor of Anthropology, Harvard University. His subject will be "Hip-Hip-Hippocrates, or An Anthropological Cheer for Medicine."

All members of the College, physicians of Boston and visitors attending the Session with their families and friends, are cordially invited. Table reservations for groups may be arranged. Music will be furnished by Ruby Newman and his orchestra. Tickets should be purchased at the Registration Bureau by Wednesday afternoon—price, $4.00.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The wives of the Boston members of the College cordially invite all the visiting women at the College meeting in Boston to participate in the special program of entertainment arranged for them. A postal card will be sent with the final Program, in order that advanced intentions may be indicated.

The visiting women are asked to register immediately upon arrival in Boston at their Headquarters in Room 419 of the Hotel Statler. There they will receive a program of entertainment and information about theaters, restaurants, stores and places of interest in and around Boston.

It is necessary to make reservations for some of the events on the Ladies' Program.

MONDAY, APRIL 21, 1941

Morning: Registration, Room 419, Hotel Statler.

Afternoon: 4:00 to 6:00 p.m. Welcoming Tea at the Women's City Club, 40 Beacon Street.

Evening: Free for theater, movies, bridge.

TUESDAY, APRIL 22, 1941

Morning: Free.

Afternoon: 1:15 p.m. Buses leave Hotel Statler for short visit to Harvard University with guide service through Harvard Yard, the Memorial Chapel, Widener Library, the Fogg Museum, the Peabody Museum (glass flowers) and one of the Houses.

3:30 p.m. Buses leave Cambridge for the home of Mrs. Arthur Lyman in Waltham where we are to be her guests at Tea.

4:30 to 5:00 p.m. Buses return to Hotel Statler. Bus fare, $1.00.

Evening: 9:00 p.m. Concert at Symphony Hall by Boston Symphony Orchestra for the members of the American College of Physicians and their wives, at the invitation of Dr. Serge Koussevitzky, Conductor.

WEDNESDAY, APRIL 23, 1941

Morning: Free.

Afternoon: 1:30 p.m. Buses leave for the Isabella Gardner Museum and conducted tour of the Palace, followed by music and tea in the Tapestry Room as guests of the College. Return at 4:30 to Hotel Statler. Bus fare, $.50.

Evening: 8:30 p.m. Convocation, President's Reception and Dance in the Ballroom, Hotel Statler. Ruby Newman and orchestra.

THURSDAY, APRIL 24, 1941

Morning: Free.

Afternoon: 1:00 p.m. Lunch and Fashion Show by Hickson in the main dining room, Hotel Ritz-Carlton. Luncheon a la carte ($1.25 minimum).

Evening: 8:00 p.m. Annual Banquet of the College in the Ballroom, Hotel Statler. Ruby Newman and orchestra.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the mezzanine floor of the Hotel Statler. From the accompanying diagram it will be noted that the Exhibit is widely extended because of the facilities available, but actually the total exhibit space is not as great as customary. Members are urged to familiarize themselves with the Exhibit layout and to make it a point to visit all the exhibitors, but especially is it requested that the attending physicians make a particular effort to visit the exhibits, numbers 1 to 24, which are somewhat removed from the main course of travel.

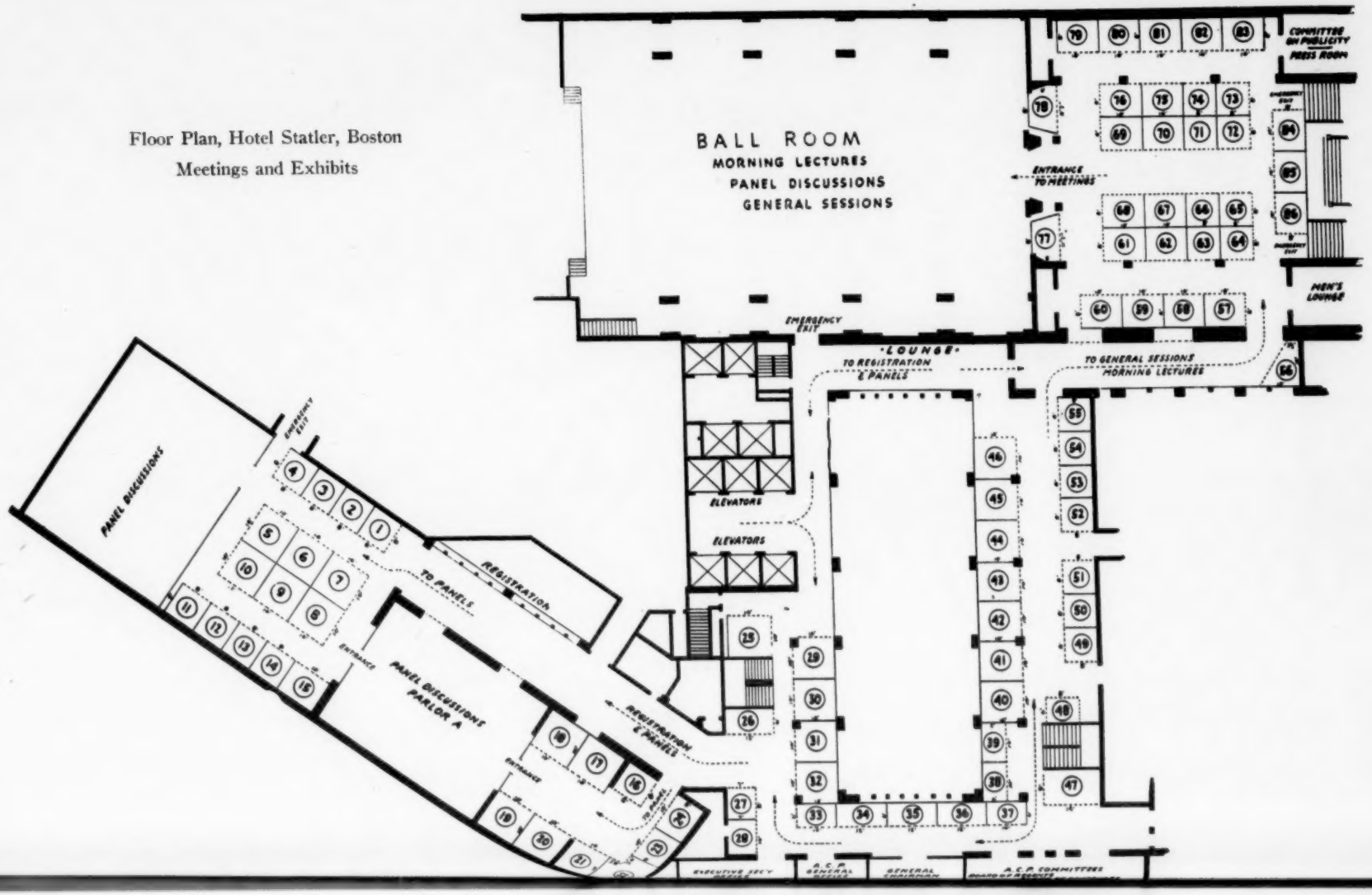
The College has put forward an organized effort to raise the standards of the technical exhibits. All irrelevant products have been eliminated and only firms are invited who shall present a group of approved products of scientific interest to Internal Medicine and its allied specialties. Members of the College will readily distinguish the difference between this Exhibit and the general medical exhibit elsewhere where frequently all sorts of irrelevant products are displayed, "catch-penny" exhibits accepted, and where methods of high-pressure selling are common. The Exhibit sponsored by our College warrants the respect and interest of every attending physician. Here conveniently assembled will be the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice. These exhibitors and their displays merit your special attention, not only because of their educational value, but because of their contributions to the support of the Annual Sessions of the College.

Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

LIST OF EXHIBITORS

	Booth No.
White Laboratories, Inc., Newark, N. J.	1
J. H. Emerson Company, Cambridge, Mass.	2–3
Gradwohl Laboratories, St. Louis, Mo.	4
The Wm. S. Merrell Company, Cincinnati, Ohio	5
Hanovia Chemical & Mfg. Company, Newark, N. J.	6
Jones Metabolism Equipment Co., Chicago, Ill.	7
Carnation Company, Oconomowoc, Wis.	8–9
Unassigned	10
Abbott Laboratories, North Chicago, Ill.	11
Duke Laboratories, Inc., Stamford, Conn.	12
American Heart Association, New York, N. Y.	13
Mallinckrodt Chemical Works, St. Louis, Mo.	14
Sandoz Chemical Works, Inc., New York, N. Y.	15
S. H. Camp & Company, Jackson, Mich.	16
Schering Corporation, Bloomfield, N. J.	17
The New York Medical Exchange, New York, N. Y.	18
Ciba Pharmaceutical Products, Inc., Summit, N. J.	19–20
Cameron Heartometer Co., Chicago, Ill.	21
Ritter Equipment Co., Inc., Rochester, N. Y.	22
American Hospital Supply Corporation, Chicago, Ill.	23

Floor Plan, Hotel Statler, Boston
Meetings and Exhibits



Kellogg Company, Battle Creek, Mich. 24
Mead Johnson & Company, Evansville, Ind. 25
Medical Case History Bureau, New York, N. Y. 26
Laboratoire Nativelle, New York, N. Y. 27
Cambridge Instrument Co., Inc., New York, N. Y. 28
General Electric X-Ray Corporation, Chicago, Ill. 29–30
Paul B. Hoeber, Inc., New York, N. Y. 31
John Wyeth & Brother, Inc., Philadelphia, Pa. 32
Davies, Rose & Company, Ltd., Boston, Mass. 33
Year Book Publishers, Chicago, Ill. 34
E. R. Squibb & Sons, New York, N. Y. 35
Williams & Wilkins Company (William Wood Books), Baltimore, Md. 36
Parke, Davis & Company, Detroit, Mich. 37
Eli Lilly and Company, Indianapolis, Ind. 38–39–40
Frederick Stearns and Company, Detroit, Mich. 41
Allergia Products Co., Newton, Mass. 42
The Medical Bureau, Chicago, Ill. 43
Winthrop Chemical Company, Inc., New York, N. Y. 44
Lea & Febiger, Philadelphia, Pa. 45
The E. L. Patch Co., Boston, Mass. 46
Picker X-Ray Corporation, New York, N. Y. 47
W. A. Baum Co. Inc., New York, N. Y. 48
The Macmillan Company, New York, N. Y. 49–50
The Arlington Chemical Company, Yonkers, N. Y. 51
Vegex, Incorporated, New York, N. Y. 52
The Blakiston Company, Philadelphia, Pa. 53
J. B. Lippincott Company, Philadelphia, Pa. 54–55
LaMotte Chemical Products Company, Baltimore, Md. 56
Sanborn Company, Cambridge, Mass. 57
Taylor Instrument Companies, Rochester, N. Y. 58
Merck & Co. Inc., Rahway, N. J. 59–60
W. B. Saunders Company, Philadelphia, Pa. 61
The G. F. Harvey Company, Saratoga Springs, N. Y. 62
D. Appleton-Century Company, Inc., New York, N. Y. 63
F. A. Davis Company, Philadelphia, Pa. 64
Riedel-de Haen, Inc., New York, N. Y. 65
Smith, Kline & French Laboratories, Philadelphia, Pa. 66–67
The Muller Laboratories, Baltimore, Md. 68
Devereux Schools, Devon, Pa. 69
H. J. Heinz Co., Pittsburgh, Pa. 70–71
Bilhuber-Knoll Corp., Orange, N. J. 72
Gerber Products Company, Fremont, Mich. 73
S. M. A. Corporation, Chicago, Ill. 74
Oxford University Press, New York, N. Y. 75
The Maltine Company, New York, N. Y. 76
Cameron Surgical Specialty Co., Chicago, Ill. 77
Warren E. Collins, Inc., Boston, Mass. 78
The C. V. Mosby Company, St. Louis, Mo. 79
Becton, Dickinson & Co., Rutherford, N. J. 80–81
Kalak Water Co. of New York, Inc., New York, N. Y. 82
Ayerst, McKenna & Harrison (U. S.) Ltd., Montreal, Que. 83
Lederle Laboratories, Incorporated, New York, N. Y. 84–85–86

OUTLINE OF THE BOSTON SESSION

Hotel Statler events are indicated in **bold type**

TIME	MONDAY	TUESDAY		WEDNESDAY		THURSDAY		FRIDAY	
	April 21	April 22		April 23		April 24		April 25	
9:00 a.m. to 11:30 a.m.	Morning free **Registration, Exhibits, etc.**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**
12:00 m. to 1:15 p.m.		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**	
1:15 p.m. to 2:15 p.m.	Luncheon	Luncheon		Luncheon		Luncheon		Luncheon	
2:15 p.m. to 5:00 p.m.	**1st General Session**	**3d General Session**		**4th General Session**		**5th General Session** **Annual Business Meeting**		**6th General Session**	
5:00 p.m. to 8:00 p.m.	Dinner	Dinner		Dinner					
8:00 p.m. to 11:00 p.m.	**2d General Session** followed by SMOKER	8:45 Symphony Concert		**CONVOCATION,** followed by President's Reception		ANNUAL BANQUET			

GENERAL SESSIONS

The program of the General Sessions has been developed in accordance with suggestions from a large number of members with widely diversified interests. Inasmuch as these suggestions fell into certain divisions, it seemed appropriate as well as expedient to set up most of the General Sessions in the form of symposia.

The Session on Military Medicine and that on Nutritional and Metabolic Diseases seem fully justified by the necessities of the National Defense Program and the preparation for probable needs of the civilian population consequent upon a diversion from peace time activities. The Surgeons General of the Army, Navy and Public Health Services have graciously consented to be with us and present an accounting of progress in National preparedness.

That part of the General Sessions devoted to Education should serve to reaffirm the position of the College in this field, as well as to clarify its objectives.

GENERAL SESSIONS PROGRAM

Ballroom, Hotel Statler

FIRST GENERAL SESSION

Monday Afternoon, April 21, 1941

General Chairman William B. Breed, presiding

p.m.

2:15 Addresses of Welcome:

WILLIAM B. BREED, F.A.C.P., General Chairman, Twenty-fifth Annual Session, Boston, Mass.

WALTER G. PHIPPEN, President of the Massachusetts Medical Society.

FRANK H. LAHEY, President-Elect of the American Medical Association.

The Honorable MAURICE J. TOBIN, Mayor of Boston.

The Honorable LEVERETT SALTONSTALL, Governor of Massachusetts.

JAMES B. CONANT, President of Harvard University.

Response to Addresses of Welcome:

JAMES D. BRUCE, F.A.C.P., President of the American College of Physicians; Vice President in Charge of University Relations, University of Michigan; Ann Arbor, Mich.

3:30 INTERMISSION.

President James D. Bruce, presiding

4:00 The Responsibility of the Hospital Staff in Graduate Medical Education.

FRANK J. SLADEN, F.A.C.P., Lecturer in Postgraduate Medicine, University of Michigan; Physician-in-Chief of Henry Ford Hospital, Detroit, Mich.

4:20 The American Board of Internal Medicine as a Factor in Scholarship in American Medicine.

ERNEST E. IRONS, F.A.C.P., Clinical Professor of Medicine and Chairman of Department, Rush Medical College; Chairman, American Board of Internal Medicine; Chicago, Ill.

4:40 The Responsibility of the American College of Physicians for Postgraduate Training.

EDWARD L. BORTZ, F.A.C.P., Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine; Chairman, Advisory Committee on Postgraduate Courses, American College of Physicians, Philadelphia, Pa.

5:00 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, April 21, 1941

Presiding Officer

Roger I. Lee, F.A.C.P., Boston, Mass.

p.m.

8:00 Results in the Medical Management of Bleeding Ulcer.
T. GRIER MILLER, F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

8:15 The Results of Surgical Treatment of Ulcerative Colitis.
HENRY W. CAVE (by invitation), Assistant Clinical Professor of Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.

8:30 Sinusitis and Bronchiectasis. A New Interpretation.
HERMAN H. RIECKER, F.A.C.P., Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

8:45 The Value of Sternal Marrow Aspiration as a Method of Bone Marrow Biopsy.
ERNEST H. FALCONER, F.A.C.P., Clinical Professor of Medicine, University of California Medical School, San Francisco, Calif.

9:00 The Rôle of the Vertebral Veins in Metastatic Processes.
OSCAR V. BATSON (by invitation), Professor of Anatomy, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, Pa.

9:15 Fat Metabolism in Diabetes Mellitus.
WILLIAM C. STADIE (by invitation), Associate Professor of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

9:40 ADJOURNMENT.

10:00 o'Clock

SMOKER

Ballroom, Hotel Statler

Program—Food, fun, friendship, refreshments and music. Admission by registration badge.

THIRD GENERAL SESSION

Tuesday Afternoon, April 22, 1941

Presiding Officer

Robert A. Cooke, F.A.C.P., New York, N. Y.

SYMPOSIUM ON DISEASES OF CIRCULATION

p.m.

2:15 William Withering. His Contribution to Medicine.
JONATHAN C. MEAKINS, F.A.C.P., Professor of Medicine, McGill University Faculty of Medicine, Montreal, Que., Canada.

2:40 Anticipation and Diagnosis of the Effort Syndrome (Irritable Heart).
JOHN T. KING, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

3:00 Silent or Atypical Coronary Occlusion.
WILLIAM D. STROUD, F.A.C.P., Professor of Cardiology, University of

Pennsylvania Graduate School of Medicine, Philadelphia, Pa., and JOSEPH A. WAGNER (by invitation), Morris W. Stroud, Jr., Fellow in Cardiology, Pennsylvania Hospital, Philadelphia, Pa.

3:20 INTERMISSION.

4:00 The Chemotherapy of Sub-Acute Bacterial Endocarditis.
RALPH KINSELLA, F.A.C.P., Professor of Medicine, St. Louis University, St. Louis, Mo.

4:20 Kidney Extract in the Treatment of Experimental and Clinical Hypertension.
IRVINE H. PAGE (Associate, A.C.P.), Director, Lilly Laboratory for Clinical Research, Indianapolis, Ind.

4:40 Physiology of the Early Manifestations of Left Heart Failure.
C. SIDNEY BURWELL, F.A.C.P., Research Professor of Clinical Medicine and Dean of the Faculty of Medicine, Harvard Medical School, Boston, Mass.

5:00 ADJOURNMENT.

FOURTH GENERAL SESSION

Wednesday, April 23, 1941

Presiding Officer

James G. Carr, F.A.C.P., Chicago, Ill.

SYMPOSIUM ON NUTRITIONAL AND METABOLIC DISEASES

p.m.

2:15 The National Nutrition Program.
RUSSELL M. WILDER, F.A.C.P., Professor of Medicine and Nutrition, and Chief of Department of Medicine, University of Minnesota (Mayo Foundation), Rochester, Minn.; Chairman, Committee on Food and Nutrition, National Research Council, Washington, D. C.

2:35 Food Rationing in the Armed Forces.
LT. COL. PAUL LOGAN (by invitation), Quartermaster Corps, The Army Industrial College, Washington, D. C.

2:55 Insulin and Protamine Zinc Insulin in the Management of Diabetes.
EDWARD H. MASON, F.A.C.P., Associate Professor of Medicine, McGill University Faculty of Medicine, Montreal, Que., Canada.

3:15 Protein Derivatives as Factors in Allergy.
ROBERT A. COOKE, F.A.C.P., Assistant Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

3:35 INTERMISSION.

4:00 Chemistry of Vitamin K.
LOUIS F. FIESER (by invitation), Professor of Chemistry, Harvard University, Cambridge, Mass.

4:20 The Clinical Symptoms and Signs of Vitamin B Complex Deficiency.
WILLIAM H. SEBRELL, JR. (by invitation), Chief, Division of Chemotherapy, U. S. Public Health Service, Washington, D. C.

4:40 The Syndrome of Multiple Vitamin Deficiency.
V. P. SYDENSTRICKER, F.A.C.P., Professor of Medicine, University of Georgia School of Medicine; Physician-in-Chief, University Hospital, Augusta, Ga.

5:00 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 23, 1941

8:30 o'Clock

Ballroom, Hotel Statler

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. The President's Address.
   James D. Bruce.
2. Presentation of Newly-Elected Fellows and Recital of the Pledge.
   George Morris Piersol, Secretary-General.
3. Presentation of John Phillips Memorial Medal for 1940–41.
4. Announcement of Research Fellows of the College for 1941.
5. Convocational Address:
   JAMES ALEXANDER MILLER, F.A.C.P., Former President of the American College of Physicians, New York, N. Y.

President's Reception

The Reception and Dance will follow one-half hour after the completion of this program, and will be held in the Ballroom of the Hotel Statler. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

FIFTH GENERAL SESSION

Thursday Afternoon, April 24, 1941

Presiding Officer

O. H. Perry Pepper, F.A.C.P., Philadelphia, Pa.

SYMPOSIUM ON MILITARY MEDICINE

p.m.

2:00 The United States Army.
SURGEON GENERAL JAMES C. MAGEE (Major General, M.C.), U.S.A. (F.A.C.P.)

2:20 The United States Navy.
SURGEON GENERAL ROSS T. MCINTIRE (Rear Admiral, M.C.), U.S.N. (F.A.C.P.).

2:40 The United States Public Health Service.
SURGEON GENERAL THOMAS PARRAN, U. S. Public Health Service (F.A.C.P.).

3:00 Industrial Hygiene in the National Defense Program.
PAUL A. NEAL, U. S. Public Health Service (by invitation), and J. J. BLOOMFIELD, U. S. Public Health Service (by invitation).

3:20 The Control of Infectious Diseases in Rapidly Mobilized Troops.
LT. COL. A. P. HITCHENS, M.C., U.S.A. (F.A.C.P.); Professor of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

3:40 INTERMISSION.

4:00 The Development of Plasma Preparations for Transfusions.
MAX STRUMIA (by invitation), Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
4:20 Special Medical Service in the Defense Program.
COMMANDER C. S. STEPHENSON, M.C., U.S.N. (By invitation.)
4:40 The Recruit's First Year.
LT. COL. PATRICK S. MADIGAN, M.C., U.S.A. (F.A.C.P.).
5:00 ADJOURNMENT, to be followed immediately by

THE ANNUAL BUSINESS MEETING

All Masters and Fellows are urged to be present. Annual reports of the Secretary General, Executive Secretary and Treasurer will be presented; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. Roger I. Lee, Boston, Mass., will be inducted into office.

THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, 8:00 o'Clock

Ballroom, Hotel Statler

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: William B. Breed, F.A.C.P., Boston, Mass.
Address: "Hip-Hip-Hippocrates, or An Anthropological Cheer for Medicine."
Earnest Albert Hooton, Ph.D., B.Litt., Sc.D., Professor of Anthropology, Harvard University.

SIXTH GENERAL SESSION

Friday, April 25, 1941

Presiding Officer

Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md.

SYMPOSIUM ON INFECTIOUS DISEASES

p.m.
2:15 Influenza.
FRANK L. HORSFALL, JR. (by invitation), International Health Division, The Rockefeller Institute for Medical Research, New York, N. Y.
2:30 Rheumatic Heart Disease in Southern Climates.
GEORGE R. HERRMANN, F.A.C.P., Professor of Clinical Medicine, University of Texas School of Medicine, Galveston, Texas;
GEORGE M. DECHERD, JR. (F.A.C.P.), Associate Professor, University of Texas School of Medicine, Galveston, Texas, and
J. T. ROBERTS (by invitation), Assistant Professor, University of Texas School of Medicine, Galveston, Texas.
2:45 Management of Pneumonias Associated with Pneumococci of the Higher Numbered Types.
HOBART A. REIMANN (by invitation), Professor of Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

3:00 Mass Immunization against Typhus Fever.
R. E. DYER (by invitation), Chief, Division of Infectious Diseases, U. S. Public Health Service, Washington, D. C.

3:15 Screening for Tuberculosis in a Civilian Population by Fluorography.
BRUCE H. DOUGLAS (F.A.C.P.), Controller of Tuberculosis, Detroit Health Department, Detroit, Mich., and
CARL C. BIRKELO (by invitation), Detroit, Mich.

3:35 INTERMISSION.

4:00 Treatment of Cardiovascular Syphilis.
UDO J. WILE, F.A.C.P., Professor of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Mich.

4:15 Scarlet Fever Immunization.
JOHN A. TOOMEY, F.A.C.P., Professor of Clinical Pediatrics and Contagious Diseases, Western Reserve University School of Medicine, Cleveland, Ohio.

4:30 The Diagnosis and Management of Brucellosis.
WALTER M. SIMPSON, F.A.C.P., Director, Kettering Institute for Medical Research; Diagnostic Laboratories, Miami Valley Hospital, Dayton, Ohio.

4:45 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures are in response to increasing interest in fundamental problems and are planned to relate as closely as possible to the subject matter of the General Sessions.

They will be held daily, Tuesday through Friday, from 9:30 to 11:30 a.m., in the Ballroom of the Hotel Statler.

The lectures will be open to all members and guests of the College.
Admission by regular registration badge.

Tuesday Morning, April 22, 1941

Ballroom, Hotel Statler

Presiding Officer

D. Sclater Lewis, F.A.C.P., Montreal, Que.

a.m.

9:30 The Development and Present Status of the Precordial Electrocardiogram.
FRANK N. WILSON, F.A.C.P., Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

10:30 Peripheral Circulation Failure Mechanisms.
CARL J. WIGGERS, F.A.C.P., Professor of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio.

Wednesday Morning, April 23, 1941

Ballroom, Hotel Statler

Presiding Officer

William J. Kerr, F.A.C.P., San Francisco, Calif.

a.m.

9:30 Plasma Proteins in Disease.
ROBERT F. LOEB, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

10:30 The Clinical Implications of Sodium, Chloride and Potassium Metabolism.
GEORGE W. THORN, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

11:00 The Clinical Implications of Phosphorus and Calcium Metabolism.
DAVID P. BARR, F.A.C.P., Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

Thursday Morning, April 24, 1941

Ballroom, Hotel Statler

Presiding Officer

Charles Hartwell Cocke, F.A.C.P., Asheville, N. C.

a.m.

9:30 The Autonomic Nervous System.
WALTER B. CANNON (by invitation), Professor of Physiology, Harvard University Medical School, Cambridge, Mass.

10:30 The Hypothalamic Area.
PHILIP BARD (by invitation), Professor of Physiology, Johns Hopkins University School of Medicine, Baltimore, Md.

Friday Morning, April 25, 1941

Ballroom, Hotel Statler

Presiding Officer

George Morris Piersol, F.A.C.P., Philadelphia, Pa.

a.m.

9:30 The Epidemiology and Immunological Factors in Hemolytic Streptococcus Diseases.
FRANCIS G. BLAKE, F.A.C.P., Professor of Medicine, Yale University School of Medicine, New Haven, Conn.

10:30 Progress in the Diagnosis of Certain Virus Diseases.
THOMAS FRANCIS, JR. (by invitation), Professor of Bacteriology, New York University College of Medicine, New York, N. Y.

PANEL DISCUSSIONS

The Panel Discussions have been selected after careful consideration of topics which are of the greatest practical value to the physicians. Panel Discussers will gather from all parts of the country, and will be men who are not only highly qualified in their specialties, but who possess the capacity to discuss the specific questions clearly and concisely.

The Panel Discussions will be held from 12:00 m. to 1:15 p.m., daily, Tuesday through Friday at the Hotel Statler, except on Tuesday and Wednesday when one discussion will be held at the Hotel Copley Plaza.

The leaders will discuss special phases of the subject which have been assigned to them. Admission to the Panels will be by ticket. Application forms will accompany the formal program when later mailed to all members. When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. The discussers will answer those questions which seem to be most in demand.

CLINICS

Clinics will be held at each of the Boston hospitals during the mornings of the Annual Session. Each clinic will begin promptly at nine o'clock and the clinical morning will end with equal promptness at 11:30, in order to allow those who wish to attend the Panel Discussions to reach the meeting place on time.

The clinics will be true clinics. Each individual who holds one will himself give the history of the patients he presents, will demonstrate the essential physical findings, will establish his own diagnosis, and will outline the treatment and prognosis. In this manner it is hoped that the morning exercises will be truly practical and unmistakably clinical in nature.

For those interested in clinical-pathological correlation there will be one exercise each morning at the Harvard Medical School. This will be of two types: A Roentgen-Ray Conference at which roentgen-ray films will be demonstrated along with very short case histories, and the radiologist, faced with a film which he has never before seen, will establish his diagnosis, explaining his reasoning to the audience. His diagnosis will be confirmed or proved wrong by the pathologist.

There also will be more orthodox clinical-pathological conferences. A case report will be forwarded to each clinician who has been selected to lead a conference, and he will attempt to establish the diagnosis on his case from the data submitted to him. The diagnosis will be confirmed or proved wrong by the pathologist. Those interested in this form of exercise and wishing to have the case histories in their hands for study before the conferences are held may do so by notifying Dr. Reginald Fitz, Chairman, 319 Longwood Avenue, Boston.

PANEL DISCUSSIONS—12:00 M.–1:15 P.M.

Tuesday April 22	DISORDERS OF THE BLOOD *George R. Minot Charles A. Doan Claude E. Forkner Russell L. Haden	INTERPRETATION AND TREATMENT OF SYMPTOMS *John H. Musser Soma Weiss	BRIGHT'S DISEASE AND HYPERTENSION *Warfield T. Longcope A. M. Fishberg James P. O'Hare	NUTRITIONAL DEFICIENCIES *V. P. Sydenstricker Tom D. Spies Wm. B. Castle	PERIPHERAL VASCULAR DISEASE *Wallace M. Yater Richard B. Capps John Homans
Wednesday April 23	DISEASES OF THE CORONARY ARTERY *Robert L. Levy Samuel A. Levine Wm. D. Stroud	SULFANILAMIDE AND RELATED COMPOUNDS *Perrin H. Long Eli K. Marshall, Jr. Charles A. Janeway	EPILEPSY AND MIGRAINE *William G. Lennox Tracy J. Putnam	ESTIMATION OF SURGICAL RISK *Louis Hamman Frank H. Lahey	PNEUMONIA AND MENINGITIS *Francis G. Blake J. G. M. Bullowa Maxwell Finland
Thursday April 24	ALLERGY *Robert A. Cooke Francis M. Rackemann Richard A. Kern	ARTHRITIS *Walter Bauer W. Paul Holbrook Philip S. Hench	ELECTROCARDIOGRAPHY *Arlie R. Barnes Paul D. White Frank N. Wilson	GASTRO-INTESTINAL PROBLEMS *Walter C. Alvarez Chester M. Jones	SYPHILIS AND ITS TREATMENT *Paul A. O'Leary Harold T. Hyman
Friday April 25	CONTAGIOUS DISEASES *Conrad C. Wesselhoeft John R. Paul Edwin H. Place	DOSAGES OF AND TOXIC REACTIONS TO DRUGS *Walter A. Bastedo Theodore G. Klumpp Harry Gold	PHYSIOLOGICAL ASPECTS OF HEART DISEASE *C. Sidney Burwell Carl J. Wiggers	ENDOCRINES *George W. Thorn Fuller Albright J. S. L. Browne	TUBERCULOSIS *J. Burns Amberson, Jr. Donald S. King Bruce H. Douglas

* Chairman.

BOSTON AS A MEDICAL CENTER

BOSTON may fittingly introduce herself to the American College of Physicians as a hostess whose medical activities have matured. This choice of expression does not arise as much from the storied reticence of the Back Bay as it does from the thought that in her colonial days Boston may have had opportunities for medical reflection which have ripened over the years into accepted and well developed practices. Thus we may trace her present literary proclivities back through the one hundred and thirteen years of the New England Journal of Medicine, through such earlier publications as those of Benjamin Waterhouse on vaccination, and the still earlier efforts of Zabdiel Boylston and Cotton Mather on inoculation, finally getting back to 1677, when the first medical publication in this country appeared under the delineating title: "*A Brief Rule, to guide the common people of New England How to Order Themselves and theirs in the Small Pocks, or Measels.*" This took the form of what used to be called a broadside, and was signed by "*a Friend, Reader to thy Welfare, Thomas Thacher.*" Dr. Thacher was a clergyman, but those who have taken over his concern for the health of the common people here wish to continue his solicitude toward his readers, and to express the hope that circumstances will permit many of our present readers to visit us in April.

Copies of the Brief Rule may be seen at the Boston Medical Library, together with other Colonial papers, such as Governor Winthrop's receipt book in which the prescriptions for emetics don't need to be concocted and swallowed, but merely read, to be effective. The buildings of the Boston Medical Library harbor 185,000 volumes, contain reading, study and assembly rooms, the offices of the Massachusetts Medical Society, and the editorial rooms of the New England Journal of Medicine and of the Journal of Bone and Joint Surgery. Sprinkled through the City and its suburbs there are larger staffs, more eminent individuals, and grander piles of masonry by far, but the common medical touch has nowhere been more carefully retained than in the services and uses to which these organizations devote themselves at "8 The Fenway."

The approval of the Council on Medical Education of the American Medical Association is given to three medical schools in Boston: those of Boston University, of Harvard University and of Tufts College. Altogether these three schools graduate about two hundred and seventy-five physicians each year. They are the medical components of a much vaster educational output, which includes the graduates of such well known institutions as Boston College, Boston University, Emmanuel College, Harvard University, Massachusetts Institute of Technology, Radcliffe College, Regis College, Simmons College, Tufts College and Wellesley College. More than 18 per cent of the diplomates of the National Board of Medical Examiners received

GROUP I. (Boston Medical Schools.)

1. Harvard Medical School. 2. Tufts College Medical School.
3. Boston University School of Medicine.

their medical education in Boston. The three medical schools coöperate in many ways. For example, Harvard's Department of Legal Medicine, the only full time department devoting itself to this subject in the country, makes its courses available to the students of all three schools, and instruction is participated in by members of the several faculties.

The first public health regulation on the North American continent was made in 1647 when "*all our own or othr vessels comeg from any pts of ye West Indies to Boston harbor shall stop and come to an anchor before they come at ye Castle, undr ye poenalty of 100£, and that no pson comeing in any vessell from the West Indies shall go a shore in any towne, village, or farme, or come within foure rods of any othr prson,*" etc. In 1849 the General Court of Massachusetts authorized a commission to prepare a sanitary survey of the State, the result of which was the famous Lemuel Shattuck report of 1850. This report recommended the creation of a State Department of Public Health, which was established a few years later. Without counting milestones or recounting priorities, it is fair to say that Massachusetts has always had an active and progressive administration of public health. Focused as it is at the State House in Boston, this administration has often been an integral part of the educational side of public health. The Harvard School of Public Health, as well as Departments of Health or Preventive Medicine, or Hygiene, or Sanitation in other institutions have all provided a generous educational opportunity in this field. In recent years there has been developing a correlation between these various departments which tends to place the facilities of all at the disposal of each. A senior student in any of the approved medical schools in Boston, for example, may arrange to spend his time at the Harvard School of Public Health, provided he gives evidence of his particular interest and qualification in this direction.

The administration of public health in the City of Boston has been expanded in the past decade by the establishment of district health units, housed in buildings built by the White Fund, and operated by the City. The result has been a decentralization of activities which has facilitated the organization of preventive and welfare clinics. This has provided another opportunity for medical school affiliation, as well as the more effective accomplishment of public health functions, and these health units are now utilized for instruction in both the graduate and undergraduate departments of the medical schools.

The scope of opportunity for graduate medical study in Boston may best be indicated by listing the available institutions and their facilities. These are mentioned as in the last lists approved by the Council on Medical Education and Hospitals of the American Medical Association. Inaccuracies in the compilation, if present, may be due to the fact that revision is continually taking place. Many readers will be able to season this list with reminiscences

GROUP II. (Boston Hospitals.)

(Approved by the American Medical Association for Residencies and Internships.)

4. Massachusetts General Hospital. 5. Peter Bent Brigham Hospital. 6. U. S. Marine Hospital. 7. Massachusetts Memorial Hospital.

of their own hospital days, and will be able to see evidence of the continual expansion that has been taking place.

BETH ISRAEL HOSPITAL: Internships. Residencies or Fellowships in Medicine, Otolaryngology, Radiology, Surgery and Urology.

BOSTON CITY HOSPITAL: Internships. Residencies or Fellowships in Anesthesia, Communicable Diseases, Dermatology and Syphilology, Medicine, Neurology, Neurosurgery, Obstetrics and Gynecology, Ophthalmology and Otolaryngology, Orthopedic Surgery, Pathology, Pediatrics, Radiology, Surgery, Thoracic Surgery, Tuberculosis and Urology.

BOSTON FLOATING HOSPITAL: Residencies in Pediatrics.

BOSTON LYING-IN HOSPITAL: Residencies in Obstetrics and Pathology.

CARNEY HOSPITAL: Internships. Residencies in Obstetrics and Gynecology.

CHILDREN'S HOSPITAL: Residencies and Fellowships in Orthopedic Surgery, Pathology, Pediatrics, Radiology and Surgery.

COLLIS P. HUNTINGTON MEMORIAL HOSPITAL: Residency and Fellowships in Malignant Disease.

FAULKNER HOSPITAL: Internships.

FREE HOSPITAL FOR WOMEN: Residencies in Gynecology.

HOUSE OF THE GOOD SAMARITAN: Residency in Cardiology.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL: Residencies in Medicine.

LAHEY CLINIC: Residencies and Fellowships in Anesthesia, Medicine, Neurosurgery, Otolaryngology, Orthopedic Surgery, Radiology, Surgery and Urology.

MASSACHUSETTS EYE AND EAR INFIRMARY: Residencies in Ophthalmology and Otolaryngology.

MASSACHUSETTS GENERAL HOSPITAL: Internships. Residencies and Fellowships in Anesthesia, Dermatology and Syphilology, Medicine, Neurology, Neurosurgery, Orthopedic Surgery, Pathology, Pediatrics, Psychiatry, Radiology, Surgery and Urology.

MASSACHUSETTS MEMORIAL HOSPITALS: Internships. Residencies and Fellowships in Anesthesia, Medicine, Obstetrics, Pathology, Radiology, Surgery and Urology.

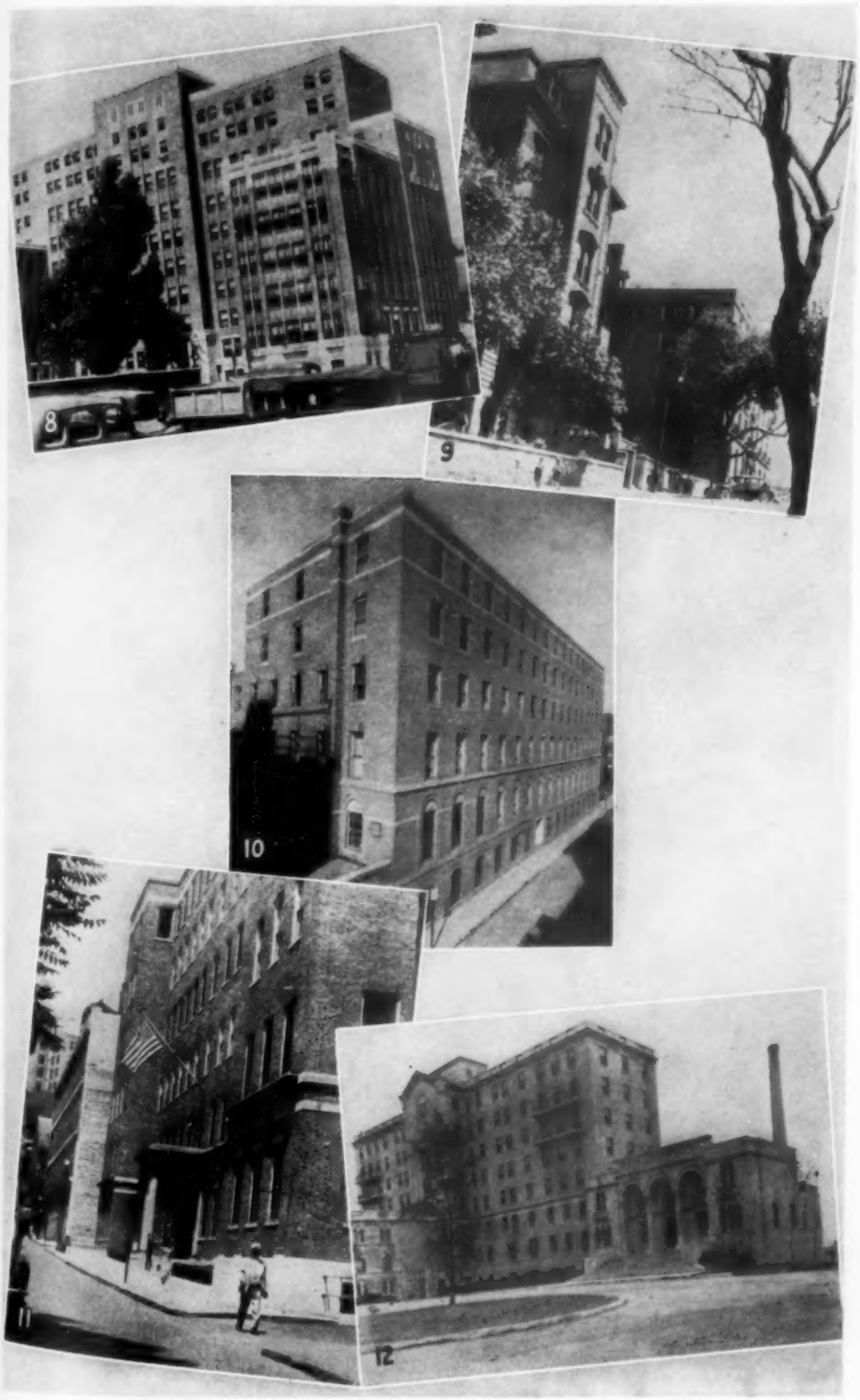
NEW ENGLAND DEACONESS HOSPITAL: Residencies in Malignant Disease, Pathology and Radiology.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN: Internships.

PETER BENT BRIGHAM HOSPITAL: Internships. Residencies in Medicine, Pathology, Radiology and Surgery.

ST. ELIZABETH'S HOSPITAL: Internships.

Outside of what is colloquially known as "Boston Proper" (for which in the above list Brookline was included and Long Island omitted), there are many other approved internship and residency opportunities, such as those at the Long Island Hospital, Chelsea Memorial Hospital, U. S. Naval Hospital, Lynn Hospital, Salem Hospital, Beverly Hospital, Cambridge Hospital, Cambridge City Hospital, Malden Hospital, Waltham Hospital, Newton Hospital, Quincy City Hospital and others. These rightfully belong in any catalogue of Medicine in Greater Boston, as do also the McLean Hospital and several of the State Institutions for the Insane, most of which provide approved residencies in psychiatry. The newly opened United States Marine Hospital is also a part of our medical life. Its opportunities for graduate education are not listed by the American Medical Association nor are those



GROUP II—*Continued*

8. Boston City Hospital.
9. Carney Hospital.
10. Boston Dispensary.
11. Joseph H. Pratt Diagnostic Hospital.
12. Beth Israel Hospital.

of several other local institutions such as the House of the Good Samaritan. Likewise 12 full time fellowships in Domiciliary Medicine at the Boston Dispensary are not listed by the American Medical Association because that is a category with which it has not as yet concerned itself. None of those professing interest in what they call "socialized medicine" in recent years has made a study of this Boston service, yet it makes over fifty thousand sick calls a year to the poor of the City! The Boston Sanitarium at Mattapan and the Middlesex Sanitarium at Waltham are available for the study of tuberculosis.

Very large outpatient clinics are of course available. One of them alone has thirty-one clinical divisions and received 171,000 visits from 26,000 people in the last calendar year. Two others are of similar proportion, and many of them are widely used for educational purposes.

In the recently promoted field of postgraduate education, for physicians already established in practice, Boston is the center for three separate and somewhat distinctive efforts. I. Harvard Medical School offers a large number of Courses for Graduates on a tuition fee basis. These courses place the facilities of the medical school in most of the basic science and clinical departments at the disposal of the profession. There is at the present time an increasing demand for such of these courses as are acceptable to the various certifying boards. II. The Massachusetts Medical Society sponsors a peripatetic program, supported largely by Federal funds, and designed to bring instruction to the doctor without asking him to leave his practice for more than a few hours at a time. The Medical Society has also jointly sponsored three postgraduate assemblies of the usual type, in which large groups are addressed by lecturers who have been carefully selected in advance. III. The third effort is that of the postgraduate division of Tufts Medical School, made possible by grants from the Bingham Associates Fund, the primary objective of which is improvement of the practice of medicine in the State of Maine. This arrangement also provides courses for technicians, dietitians and the other ancillary workers in the care of the sick. Physicians may choose between, or combine, intensive courses in the city and the peripatetic courses near home, the one variety often being designed

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GROUP III. (BOSTON'S HISTORIC VIEWS.)

13. Massachusetts State House.
14. Paul Revere House—Oldest house in Boston, built about 1660 and occupied by Paul Revere until 1800.
15. Skyline of Boston with Public Garden and Boston Common.
21. Faneuil Hall—Cradle of American Liberty because of meetings held here prior to Revolution; first presented to Boston in 1742 by Peter Faneuil for a market place and public town hall.
22. U. S. Frigate Constitution—permanently moored at Navy Yard in Charlestown; familiarly known as "Old Ironsides"; launched, 1797; was in forty engagements and never suffered defeat; restored by funds donated by school children of America.

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to complement the other. These courses are correlated at the New England Medical Center, which is the name given to an integration of the Boston Dispensary, the Floating Hospital, the Pratt Diagnostic Hospital and Tufts Medical School.

Shrines and relics of colonial life abound in Boston and the surrounding countryside, and many of our visitors will wish to visit them. The earliest building is the Fairbanks House, 1636, in Dedham. This is among the most picturesque houses in America. One of the most accurate restorations of a seventeenth century structure is that of the Old Brown House, 1663, in Watertown, while those interested in the earliest brickwork will want to see the Peter Tufts, often called the Cradock House, in Medford. Among the eighteenth century buildings is the Wayside Inn at Sudbury. In Boston itself are the Old State House, Faneuil Hall, the Old South Meeting House, the Paul Revere House and many other points of interest. Space does not permit their being mentioned here in anything more than a fragmentary list.

Boston is one of the most attractive shopping centers in the country. Its port facilities include modern piers and docks with direct highway and railroad connections and eight miles of thirty to forty foot berthing space. At the present time the port is especially busy because of the large number of manufacturing plants in New England that are engaged in completing defense assignments, for which Boston is the natural marine outlet. Those who enjoy sea voyages may wish to travel to and from the convention by the several passenger coastwise services that are available.

However our guests may elect to travel, and wherever they may elect to stay, in private homes, hotels or clubs, we wish to extend to each of them a cordial and hearty welcome. (With Thomas Thacher, we shall consider it our privilege to be *"A Friend, Reader to thy Welfare."*)

GROUP III—*Continued*

16. Old State House—here met colonial courts and legislators, the town and city governments and the General Court of the Commonwealth; John Hancock was here inaugurated first Governor of Massachusetts in 1780; in front of it occurred the burning of stamp clearances and the Boston Massacre; here were the whipping post and the stocks; contains large collection of relics.
17. Old South Meeting House—built 1729; protest meetings held here against forcing citizens into the English Navy, also to decide the fate of the hated tea tax; used by the British as a riding school during the siege of Boston; restored and used as church until 1872.
18. Bunker Hill Monument—221 feet high, on Breed's Hill within the lines of the American redoubt, center of the Battle of Bunker Hill, June 17, 1775; General Lafayette assisted at laying of corner stone, June 17, 1825.
19. Fishermen's Memorial, Gloucester—memorial to Gloucester fishermen who have lost their lives at sea.
20. Concord Bridge—"By the Rude Bridge that Arched the Flood
Their Flag to April's Breeze Unfurled
Here Once the Embattled Farmers Stood
And Fired the Shot Heard Round the World."

POST CONVENTION TOUR TO PLYMOUTH, THE PILGRIM SHORE, AND CAPE COD

THE Annual Session in Boston affords an opportunity to offer to members and friends of the College an organized, all-expense tour of historic Plymouth, the Pilgrim Shore and Cape Cod. Doctors especially are reputed to like history. This will be a tour of the cradle of history in the United States. Not only is the Cape tied up with the Pilgrims and the early settlers, but along its shores Gosnold and other discoverers sailed.

The party will leave the Hotel Statler, Boston, at 5:30 p.m., Friday, April 25 by private de luxe motor coaches and reach Plymouth, Hotel Plymouth Rock, for dinner and the night. In the morning of the 26th, Pilgrim Hall, Forefather's Monument, Burial Hill and Plymouth Rock will be visited, and after a tour of the town, the party will proceed through Sandwich, where the

Canopy over Plymouth Rock.

famous glass was made, Barnstable, Yarmouth, Dennis, Brewster and Orleans, with lunch in Provincetown. Returning in the afternoon by the South Shore, the party will pass through Chatham, Hyannis, Falmouth, glimpsing the islands of Nantucket and Martha's Vineyard, motoring along Buzzard's Bay, to return to the hotel at Plymouth for dinner and the night. On the morning of the 27th the party will visit the John Alden House, the Home and Tomb of Daniel Webster, the Old Oaken Bucket House, the Old Stone Church, the tomb of Presidents, and the Adams Mansion in Quincy, reaching Boston in time for convenient departures by trains to all points by noon.

But let our conductor, Mr. Leon V. Arnold, describe the tour—

"Probably more has been written about Plymouth, the Pilgrim Shore, and Cape Cod than any other section of the United States. Historical novels

have been numerous and fiction using its architecture, customs, and salt speech as a back-drop have always been popular.

"At five-thirty in the afternoon our private motor coach leaves the Statler Hotel taking the direct route to Plymouth where we shall have dinner and spend the night. Our hotel is located on a bluff directly overlooking the historic Plymouth Rock.

"The next morning we shall make a tour of Plymouth and see many of the reminders of the vigorous and purposeful past, Pilgrim Hall, Forefather's Monument, Burial Hill, The Howland House, 1666, the Sparrow House, 1640, William Harlow House, 1677, and many other places connected with the early settlement.

"After our tour of Plymouth we make the complete circuit of Cape Cod. The Cape is rich in dignity and quaintness. Beautiful Georgian houses drowse beneath fine old elms. The air is heavy with the smell of salt and pine. Life is not rush and bustle. Cape Cod was settled by the Pilgrims almost as early as Plymouth. It is the Old Colony.

Pilgrim Hall, Plymouth.

"Soon after entering the Cape through Sagamore we reach Sandwich which was settled in 1637. Its bounds of land were laid out by Miles Standish and John Alden who were sent as commissioners from Plymouth. Sandwich is one of those dream towns seldom realized, an early New England village so old and so perfect that you forget the modern world as you drive slowly through the great nave of spreading elms that edge the streets. Joseph Jefferson said, 'It is the handsomest town out of England.' Here, too, was the site of the famous glass factory of more than a half century ago.

"Barnstable is another old Pilgrim town. The hilly streets are shady with magnificent trees and lined with fine old houses, each a real museum piece, but delightfully liveable, between which you catch glimpses of the blue water of the harbor. James Otis, the fiery orator, was born here.

"Yarmouth is a one street town—but such a street—where house after house remains as it was built in the 18th century and now highly prized by

its 20th century owners. Yarmouth may be called one of the prettiest towns in the world.

"Dennis was named after its first minister who was noted for the 'mirthfulness of his disposition.' Here most of the houses are small, old,

The Elms in Old Sandwich.

Provincetown.

gray shingled and stand alone in their big yards. Adjoining are bayberry pastures, wooded hills, and great salt marshes. It is and always has been the center of a farming community.

" Brewster, a good old Pilgrim name, looks much like itself a century and a half ago.

" Orleans has had a long history crammed with exciting incidents. Near here Lief Ericsson is believed to have landed.

" The fields around Eastham were so fertile that they tempted almost half of the Plymouth colony to emigrate there in 1646. There was wealth in the sea, too, for Thoreau writes, ' In 1662 the town agreed that part of every whale cast ashore should be appropriated for the ministry.'

" Wellfleet still holds the flavor of its fishing days. In the years preceding the Revolution nearly every man and boy was a whaler. Scarcely an old family now remains that does not cherish a whaling log of some ancestor.

Pilgrim Monument, Provincetown.

" We pass through North Truro with its three churches ' set on a hill to be nearer God and a landmark for fishermen ' and soon reach Provincetown on the tip of the Cape.

" Provincetown is first and always a fishing village. It was here that the Mayflower first dropped anchor and here the Compact was signed. This was the first state paper in America, a simple, democratic self-imposed charter of principles that 150 years later fired the spirit and provided the will to do in the American Revolution.

" In the town the shore crowds the houses, the houses crowd the streets, and during the summer season the artists with their easels crowd everything. Commercial Street is only twenty feet wide including the sidewalk. Back

of the town are the dunes, the Desert of Provincetown, which we shall see from the top of the Pilgrim Monument.

"We shall lunch in Provincetown. The return route will be detailed in the next issue of the ANNALS.

"You have always wanted to see this historic section. You will enjoy seeing Spring in New England. It is economy of both time and money to see them now. Members as far west as Chicago can be in their offices on Monday morning."

Mr. Arnold will accompany the party. Many of the members will remember him very pleasantly in connection with the Bermuda Cruise, the New Orleans meeting, and the Post Convention trip to Mexico City.

Early reservation is necessary for the accommodation is limited. Send in your reservation now to Leon V. Arnold, 36 Washington Square West, New York City. Final payment will not be due until April 10 and even then your deposit will be returned if for any reason you must change your plans. Every necessary expense, $27.75 per person.